Approval Sheet (provided by Graduate Education on the day of public defense)

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
2002		**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Family History of Breast Cancer as a Determinant of the Risk of Developing Endometrial and Ovarian Cancers: A Nationwide Cohort Study	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **Uniformed Servicces universsity of the Health Sciences,F. Edward Herbert School of Medicine,4301 Jones Bridge Road,Bethesda,MD,20814-4799**	8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
see report

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			
unclassified	**unclassified**	**unclassified**		**194**	

The author hereby certifies that the use of any copyrighted material in the thesis manuscript entitled:

"Family history of breast cancer as a determinant of the risk of developing endometrial and ovarian cancers: A nationwide cohort study"

is appropriately acknowledged and, beyond brief excerpts, is with the permission of the copyright owner.

Niloufar Neely Kazerouni
Department of Preventive Medicine and Biometrics
Uniformed Services University of the Health Sciences

ABSTRACT

Family History of Breast Cancer as a Determinant of the Risk of Developing Endometrial and Ovarian Cancers: A Nationwide Cohort Study

N. Neely Kazerouni, Dr.P.H., 2002

Dissertation directed by Mark Greene, M.D., Catherine Schairer, Ph.D., National Cancer Institute; Heidi Friedman, Ph.D., Paul Hshieh, Ph.D., David Trump, M.D., M.P.H., Department of Preventive Medicine and Biometrics, USUHS; Dr. William Haffner, M.D., Department of Obstetrics and Gynecology, USUHS.

Statement of the problem: Although endometrial and ovarian cancers share some of the same reproductive, hormonal, and genetic risk factors with breast cancer, it is not well established if a family history of breast cancer is associated with endometrial and ovarian cancer risk in a general population setting. We examined these associations in a prospective cohort study.

Methods: The women in the endometrial (n=37,583) and ovarian (n=49,975) cancer studies were former participants in a national breast cancer screening who were selected for additional follow-up (1979-1998). During follow-up, 648 and 362 women with endometrial and ovarian cancers, respectively, were identified. We examined information on the breast cancer history of mothers, sisters, daughters, aunts, and grandmothers of the study participants as well as the number of relatives affected with breast cancer, their age at diagnosis, and breast cancer laterality. We used Poisson regression to estimate rate ratios and 95% confidence intervals to characterize the precision of these point estimates.

Results: The presence of breast cancer in a first-degree (RR=0.96, 95% CI= 0.78-1.2) or a second-degree (RR=1.0, 95% CI=0.81-1.2) relative did not influence the risk of developing endometrial cancer. In addition, the risk of endometrial cancer did not vary by age of the relative at breast cancer diagnosis or by the number of affected relatives with breast cancer. However, there was a non-significant increase in the risk of endometrial cancer among women with a 1st degree relative with bilateral breast cancer (RR=1.4, 95% CI= 0.84-2.4) but not among women with a 1st degree relative with unilateral breast cancer (RR=0.83, 95% CI=0.62-1.1). Women with a personal history of prior breast cancer were more likely to develop endometrial cancer during the course of follow-up (RR=1.3; 95% CI=1.1-1.7), but even in this subgroup, family history of breast cancer did not confer additional risk of endometrial cancer.

On the other hand, breast cancer in a first- or second-degree (RR=1.4, 95% CI=1.1-1.7), and any second-degree (RR=1.3, 95% CI=1.0-1.7) relative, increased the risk of ovarian cancer. Participants with two or more first-degree relatives with breast cancer also had a significantly increased risk (RR=1.8, 95% CI=1.1-2.8). Risk was particularly high among women with 2 or more first-degree affected relatives, at least one of whom had bilateral breast cancer (RR=4.2, 95% CI=1.7-10) or younger age (<50) at breast cancer diagnosis (RR=2.6, 95% CI=1.4-4.8), and among women with a personal history of breast cancer who also had a first-degree relative with younger age at breast cancer diagnosis (RR=3.5, 95% CI: 1.7-7.4).

Conclusions: These results provide support for the hypothesis that a family history of breast cancer is a strong predictor of the risk of developing ovarian cancer, but is not a predictor of endometrial cancer risk.

Family History of Breast Cancer as a Determinant of the Risk of Developing Endometrial and Ovarian Cancers: A Nationwide Cohort Study

by

Niloufar Neely Kazerouni

Dissertation submitted to the Faculty of the Department of Preventive Medicine and Biometrics Graduate Program of the Uniformed Services University of the Health Sciences in partial fulfillment of the requirements for the degree of

Doctor of Public Health 2002

ACKNOWLEDGEMENTS

I genuinely thank my advisors, Dr. Mark Greene and Dr. Catherine Schairer from the National Cancer Institute (NCI), and Dr. Heidi Friedman from the Uniformed Services University of the Health Sciences (USUHS), for their continuous support, scientific expertise, insightful comments, great advice, ceaseless encouragements, and belief in my success. I could not have accomplished what I have fulfilled without their supervision.

I would also like to thank the other members of my dissertation committee at USUHS – Captain David Trump, Dr. Paul Hshieh, and Captain William Haffner -- for their invaluable comments, thoughtful advice, and sincere support.

I am indebted to my colleagues at NCI – Dr. Shelia Zahm, Dr. Joseph Fraumeni, Dr. Elizabeth Maloney, Captain Linda Brown, Dr. Jay Lubin, Dr. Patricia Hartge, Dr. Nathaniel Rothman, and Dr. James Lacey -- and to all the faculty at the Department of Preventive Medicine and Biometrics at USUHS, in particular, Dr. Terry Thomas, COL Kenneth Dixon, Captain Gerald Quinnan, Captain Larry Laughlin, COL Gary Gackstetter, Dr. David Cruess, COL Arthur Lee, Dr. Deborah Girasek, COL Antoinette Whitmeyer, Dr. Patrick Carney, COL John Gardner, Dr. Michael Sheridan, Janet Anastasi, and Ellen Goldman, for all the guidance they provided throughout the years of my doctoral work.

I am grateful to Drs. Stephen Redd and Michael McGeehin, and James Rifenburg, at the Centers for Disease Control and Prevention (CDC), for their generous administrative support of the completion of my thesis work at CDC.

My gratitude to all who helped with the Breast Cancer Detection Demonstration Project and who made this project a source for many research questions to be answered.

DEDICATION

To my parents, Shouri and Shahpoor Kazerouni, brothers Behfar, Nick, and nephew Nabil, who always believed in my abilities.

TABLE OF CONTENTS

List of Tables

Appendices

The Epidemiology of Endometrial and Ovarian Cancers as They Relate to a Family History of Breast Cancer

Niloufar Neely Kazerouni

INTRODUCTION

Endometrial and ovarian cancers are the first and second most common gynecologic cancers in the United States, respectively (Boring, 1994; American Cancer Society, 2002). Ovarian cancer is also the leading cause of death among all gynecologic cancers (American Cancer Society, 2002). Both cancers are very curable when they are diagnosed in their earliest stages, but the prognosis is much poorer if these tumors are detected in a more advanced stage.

The well-established risk factors to date for endometrial cancer include exposure to unopposed estrogen, older age, nulliparity, obesity, ovarian dysfunction, and late age at menopause, while smoking, multiparity, and combination oral contraceptive use are associated with reduced risk. Aside from its association with hereditary nonpolyposis colorectal cancer (HNPCC), and probably Cowden=s syndrome, the contribution of genetic susceptibility factors to endometrial cancer has not been well studied.

The well-established risk factors to date for ovarian cancer include older age, nulliparity, Jewish ancestry (i.e., BRCA1 and BRCA2 gene mutations), family history of ovarian cancer, and mismatch repair gene mutations in families with HNPCC, while multiparity and oral contraceptive use are associated with lower risk. The contribution of genetic susceptibility factors to ovarian cancer has been extensively studied. Ovarian cancer is an integral part of the hereditary breast ovarian cancer (HBOC) syndrome (Lynch et al., 1981; Prior and Waterhouse, 1981). Inherited mutations in the genes BRCA1 and BRCA2 are responsible for most (80-90%) hereditary (i.e., germline inheritance of a mutant gene conferring autosomal dominant susceptibility with high

penetrance) ovarian cancers (Miki et al., 1994; Tavtigian et al., 1996) as well as the majority of hereditary breast cancers (i.e., families with at least four cases of either female breast cancer diagnosed at age <60 years or male breast cancer diagnosed at any age) (Ford et al., 1998).

Endometrial and ovarian cancers share common hormonal and reproductive risk factors with each other and with breast cancer. Only a few studies have addressed the association between breast cancer and endometrial cancer in families, and a shared hereditary component for the two is uncertain. Numerous studies, however, have addressed familial aggregations of breast cancer and ovarian cancer and, in the context of the HBOC syndrome, a shared genetic etiology has been demonstrated. In all of these prior studies, updated family history data throughout the study and/or detailed family history information, e.g., data on age at breast cancer diagnosis, laterality, and the number of affected relatives with breast cancer, was not available.

This report describes a prospective study of incident endometrial and ovarian cancers among former participants in the Breast Cancer Detection Demonstration Project (BCDDP), a breast cancer-screening program conducted in 27 cities throughout the United States. I assessed, separately, the relationship between the risk of endometrial cancer and the risk of ovarian cancer and the presence of a family history of **breast cancer**, using family history data collected at four different intervals during this prospective cohort study. I hypothesized that detailed analyses of these unique data on age at breast cancer diagnosis, laterality, and the number of affected relatives with breast cancer might help to clarify familial and genetic risk factors for these common gynecologic cancers.

REVIEW OF THE LITERATURE

The Epidemiology of Endometrial Cancer

Endometrial carcinoma is the most common cancer of the female reproductive organs and ranks fourth in terms of incident cancers among women in the United States (American Cancer Society, 2002). The American Cancer Society estimate that 39,300 new cases of endometrial cancer will be diagnosed and that about 6,600 women will die from this cancer in 2002. The age-adjusted incidence and mortality rates for this cancer were 21.9 and 3.3 per 100,000, respectively, from 1994 through 1998 (Ries et al., 2001). According to the U.S. Surveillance, Epidemiology, and End Results Program data (Ries et al., 2001), the incidence of endometrial cancer increases with increasing age, until it peaks between ages 75 and 79 years (107.7 per 100,000), with a median age at diagnosis of 66.

Type/histopathology of endometrial cancer:

Investigators have suggested, on the basis of clinical evidence, that there are three distinct types of endometrial cancer: types I, II, and III. Type I endometrial cancers are considered to be estrogen-related (Deligdisch and Holinka, 1987). Patients with type I disease tend to be relatively young (premenopausal or in early menopause), and to have a good prognosis. These tumors are typically well-differentiated adenocarcinomas and, less commonly, adenocanthoma, secretory, or ciliated histologic variants, and are frequently associated with endometrial hyperplasia (Boyd, 1996). Their histopathology shows a well-differentiated glandular pattern with frequent foam cells and increased

number of hormone receptors, indicating estrogen responsiveness (Bandera and Boyd, 1997).

In contrast, type II endometrial cancer, which is associated with adenosquamous, papillary serous, and clear cell histologic subtypes, occurs in relatively older postmenopausal women, in the absence of an estrogen exposure history, and has a poorer clinical prognosis than in patients with type I disease (Deligdisch and Holinka, 1987; Kurman and Norris, 1987; Bandera and Boyd, 1997).

Type III endometrial cancer occurs in patients who have an inherited predisposition for endometrial cancer (Bandera and Boyd, 1997). These women tend to develop the disease 15 years earlier than the general population, and their prognosis is thought to be more favorable than that experienced by women with sporadic endometrial cancer (Watson et al., 1994; Vasen et al., 1994). Uniform histopathologic features haven't been described for this type of endometrial carcinoma.

Risk and protective factors:

1) Non-familial and non-genetic risk factors

The classical risk factors for endometrial cancer include age, unopposed estrogen therapy, tamoxifen use, late menopause, ovarian dysfunction, obesity, diabetes mellitus (non-insulin dependent diabetes mellitus: NIDDM), and nulliparity (MacMahon, 1974; McDonald et al., 1977; Pettersson et al., 1986; Parazzini et al., 1991, 1999; Fisher et al., 1994; Elwood et al., 1997; Weiderpass et al., 1999a, 2000). Conversely, factors such as smoking (which decreases circulating estrogen levels) (Brinton et al., 1993), parity (Brinton et al., 1992; Henderson et al., 1983), and combination oral contraceptive use

(Kelsey et al., 1982; Schlesselman, 1997; Weiderpass et al., 1999b) are associated with reduced risk. It has been proposed that most of these classical risk factors operate through estrogen-mediated effects on endometrial proliferation (Key and Pike, 1988), which also involve insufficient cyclic exposure to progesterone.

Tamoxifen, which is commonly considered an antiestrogen when the breast is the target organ, has been shown to exert agonistic estrogenic effects selectively in the endometrium. Tamoxifen is the first "selective estrogen receptor modulator" (SERM), and it has been used in the treatment of all stages of breast cancer for over 20 years (Osborne, 1998). SERMs are drugs that exhibit selectivity with regard to mimicking estrogen (estrogen agonist) or counteracting the effect of estrogen (estrogen antagonist) in each of the estrogen-sensitive tissues via their interaction with the estrogen receptor (Kauffman, 1995; Gradishar, 1997; Howell, 1997). Tamoxifen mimics the desirable effects of estrogen in bone (Love, 1992; Wright, 1995) and on the lipid profile (Bertelli, 1988; Bruning, 1988; Love, 1990) and antagonizes its undesirable effects in the breast. A major drawback with regard to its SERM profile is its stimulatory effect on the endometrium, which increases the risk of endometrial cancer, an observation that has been made in both preclinical and clinical studies (Gottardis, 1988; Fornander, 1989; Fisher, 1994; van Leeuwen, 1994; Assikis, 1995; Barakat, 1999; Rutqvist, 1995; Bernstein, 1999).

It has been hypothesized that the mechanism of action of non-insulin dependent diabetes mellitus, which is characterized by insulin resistance, hyperinsulinemia, and higher levels of insulin-like growth factor I (IGF-I) is by elevating androgen and lowering sex hormone binding globulin (SHBG) levels (Kaaks, 1996). It has been

reported that hyperinsulinemia increases ovarian steroid hormone production (Poretsky and Kalin, 1987), stimulates aromatization of androgens to estrogens (Garzo and Dorrington, 1984), and suppresses circulating levels of SHBG (Nestler et al., 1991). It has also been hypothesized that insulin may enhance the effects of insulin-like growth factors, and thereby promote endometrial mitogenesis (Rutanen, 1998). The association between non-insulin dependent diabetes mellitus and endometrial cancer is thought to be independent of the effect of body mass index (BMI; obesity) (Kaaks, 1996; Parazzini et al., 1999; Weiderpass et al., 2000).

In addition, reports of the occurrence of both primary breast cancer and primary endometrial cancer (so-called "double primaries") in the same individual indicate that personal history of breast cancer may be a potential risk factor for endometrial cancer and suggest that there might be an etiologic association between these two cancers. The quantitative data on multiple primary cancers in the Connecticut and Danish population-based cancer registries indicated a 40% increase in the incidence of endometrial cancer among women whose first primary cancer occurred in the breast (Harvey and Brinton, 1985) and a 20-30% increased incidence of breast cancer following a primary cancer of the endometrium (Curtis et al., 1985; Storm and Ewertz, 1985). However, the analyses in these studies did not adjust for hormonal or reproductive risk factors. In addition, due to lack of epidemiologic studies of double primary cancers of the breast and endometrium, the basis for this association is not currently known.

It is known that endometrial and breast cancer share some of the same reproductive and hormonal risk factors, such as nulliparity, and exposure to unopposed estrogen (MacMahon et al., 1970; MacMahon, 1974; Lyon, 1975; Hoover et al., 1976; Henderson

et al., 1983; Brinton and Hoover, 1992; Brinton et al., 1992; Grady et al., 1995; Sasco, 2001). A meta-analysis of 30 studies investigating the association between hormone replacement therapy and endometrial cancer risk showed a relative risk of 2.3 (95% CI= 2.1-2.5) comparing the estrogen-users to non-users (Grady et al., 1995). In a case-control study of endometrial cancer by Weiderpass et al. (1999a), the odds ratio of estrogen use for at least 5 years compared with never use was 3.0 (95% CI= 2.0-4.4). With a considerably lower risk elevation as compared to endometrial cancer, a recent study of estrogen replacement therapy and breast cancer risk (Schairer et al., 2000) also showed increases in risk with estrogen only use (RR=1.2; CI=1.0-1.4). Additionally, in case-control studies of endometrial cancer, nulliparity is associated with a two- to three-fold increased risk (MacMahon et al., 1974; Parazzini et al., 1991; Brinton et al., 1992). An international collaborative case-control study by MacMahon et al. (1970) showed that the risk of breast cancer was 1.4 times higher among single and nulliparous married women compared to parous married women.

2) Possible genetic and familial risk factors

A) Family studies:

There have been few reports of a site-specific genetic version of endometrial cancer (i.e., families in which one observes only multiple cases of endometrial cancer and no other cancers) (Porter, 1966; Boltenberg et al., 1990; Sandles et al., 1992). Families with multiple cases of endometrial cancer only are very uncommon, in contrast to the pattern of affection in families with breast or colorectal cancer. Lynch et al. (1972) have identified families in which there are high frequencies of both breast and endometrial

cancer. They investigated the types of malignant neoplasms found in members of 34 families which had two or three members affected with breast cancer. In this study, endometrial cancer occurred in six women in five of the families. Fifteen women in these five families received a diagnosis of breast cancer. This non-quantitative, descriptive observation led them to conclude that there might exist some families in which both breast and endometrial cancer occurred excessively.

To the extent that endometrial cancer occurs in a genetic context, it appears to be as a part of the Cowden's and hereditary nonpolyposis colorectal cancer (HNPCC) syndromes, each of which also includes a predisposition to multiple different cancer types. In addition, there are data to suggest that breast cancer occurs excessively in these disorders as well. This evidence of a genetic link between endometrial and breast cancer is strongest for Cowden syndrome, which clearly predisposes affected women to breast cancer, and which recently has had endometrial cancer added to the list of syndrome-defining malignancies (Mutter et al., 2000; Eng, 2000; Risinger et al., 1996; Scott et al., 2001). Cowden syndrome includes multi-organ development of benign hamartomatous and malignant epithelial tumors, most notably breast and thyroid carcinoma (Liaw et al., 1997l; Marsh et al., 1998; Eng et al., 1998). In women with Cowden's syndrome, there is a 25-50% lifetime risk of breast cancer (Starink et al., 1986); the lifetime risk of endometrial cancer in this setting has not yet been clearly defined.

In addition, Lynch et al. (1966) and Lynch and Krush (1967) suggested the existence of the "cancer-family syndrome" (HNPCC), a disorder that is characterized primarily by an increased risk of colorectal cancer among family members. It also includes a predisposition to a variety of extra-colonic neoplasms, of which carcinoma of

the endometrium is the most common. Genetic mutations in six genes involved in DNA mismatch repair [hMSH2, hMLH1, hPMS1, hPMS2, hMSH6, and hMSH3] have been implicated as the genetic basis for this disorder, which is now known as hereditary nonpolyposis colorectal cancer (HNPCC) (Fishel et al., 1993; Leach et al., 1993; Jass et al., 1992; Nicolaides et al., 1994; Plaschke et al., 2000; Ku et al., 1999). Endometrial cancer occurs in 20-40% of women with HNPCC (Watson & Lynch, 1993; Hakala et al., 1991), and in a minority of HNPCC families, endometrial cancer is the predominant malignancy, occurring more frequently than colorectal cancer (Boltenberg et al., 1990; Lynch et al., 1994; Sandles et al., 1992). The cumulative risk of endometrial cancer among women from HNPCC families with mismatch repair gene mutations is estimated to be 60% by age 70 (Aarino et al., 1999).

The cumulative risk of **breast cancer** in these families is not well defined, and it is currently controversial as to whether breast cancer truly is one of the extra-colonic malignancies that is part of the HNPCC disease spectrum. However, there clearly are at least a few families with documented HNPCC in which there is strong molecular evidence to suggest that breast cancer is part of this disorder (Risinger et al., 1996; Scott et al., 2001). Thus, the possibility exists that breast cancer may be part of the HNPCC syndrome, perhaps on the basis of selected, very specific mutations in one of the mismatch repair genes, i.e., a genotype/phenotype effect.

B) Epidemiologic studies of family history of cancer:

There are suggestions that familial risk factors may also contribute to the development of endometrial cancer, although the literature with regard to family history of endometrial cancer or other cancers, including breast, is inconsistent. Most of the

familial studies of endometrial cancer among younger (20-54 year old) women have indicated an association with a family history of endometrial cancer (Parslov et al., 2000; Gruber et al., 1996; Schildkraut et al., 1989). That is, a family history of endometrial cancer is associated with a 2.1-to 2.7-fold-increased risk of endometrial cancer among younger women. However, this association among older women has been inconsistent (Olson et al., 1999; Parazzini et al., 1994; Nelson et al., 1993; Kelsey et al., 1982). Olson et al. (1999) showed that family history of selected cancers (e.g., endometrium, colon, or breast), combined or individually, was not an endometrial cancer risk factor in postmenopausal women, whereas Nelson et al. (1993) reported a significantly higher risk of endometrial cancer among women with a family history of any of the selected sites (i.e., uterine, breast, colon, or ovarian cancer). A case-control study of a family history of endometrial, breast and ovarian cancer and the risk of endometrial cancer by Parazzini et al. (1994) showed an odds ratio of 1.5 (95% CI= 1.0-2.3) for endometrial cancer among women with a history of endometrial cancer in first-degree relatives and no associations with a family history of breast or ovarian cancer. In the study by Kelsey et al. (1982), because of the small numbers with positive family histories, there were no conclusive results.

The Epidemiology of Ovarian Cancer

Ovarian cancer accounts for 4% of all cancers among women and is the second most common gynecologic cancer in the United States (American Cancer Society, 2002). The American Cancer Society estimate that 23,300 new cases of ovarian cancer will be diagnosed and that about 13,900 women will die from this cancer in 2002. The age-

adjusted incidence and mortality rates for this cancer were 14.5 and 7.5 per 100,000, respectively, from 1994 through 1998 (Ries et al., 2001). The risk of ovarian cancer increases with age, from 10 cases per 100,000 in the group younger than 65 years old to 55 cases per 100,000 in the 65 years old and older (Ries et al., 2001). Its incidence is highest in industrialized Western countries, but low in Japan. Only about 26% of all cases are detected at an early stage; five-year relative survival rates for women with early and advanced stages are 81% and 29%, respectively (American Cancer Society, 2002).

Pathology of ovarian cancer:

About 90% of all malignant ovarian tumors are of epithelial derivation, originating (it is thought) from cells of the surface germinal epithelium of the ovary (Altcheck et al., 1996). About 43% of epithelial ovarian tumors are serous adenocarcinomas, 15% are mucinous adenocarcinomas, 22% are endometrioid adenocarcinomas, 5% are clear cell tumors, 14% are mixed or unclassified epithelial tumors of the ovary, and 1% are transitional cell or squamous cell tumors (Altcheck et al., 1996; National Cancer Institute, 1999). There also exists an intermediate class of ovarian neoplasms, which lies somewhere between normal and clearly malignant. These neoplasms are designated "borderline" epithelial tumors (Fox, 1990), and are distinguished by an absence of ovarian stromal invasion or distant metastasis. The etiologic relationship between borderline and malignant epithelial tumors of the ovary is unclear. Finally, a variety of non-epithelial tumors may originate in the ovary. These are relatively rare, and include such entities as germ cell and sex cord/stromal tumors, sarcomas and lymphomas.

Risk and protective factors:

1) Non-familial and non-genetic risk factors

Nulliparity is considered an established risk factor for ovarian cancer, while multiparity and oral contraceptive use are associated with lower risk (Parazzini et al., 1991; Vasen et al., 1996; Ford et al., 1998). Tubal ligation and hysterectomy without oophorectomy have also been associated with reduced risk in several studies (Mori et al., 1988; Whittemore et al., 1992; Hankinson et al., 1993).

The reports on the association of some environmental/lifestyle factors and ovarian cancer risk are less consistent (Whittemore et al., 1992; Weiss et al., 1996; Mink et al. 1996). For example, there are limited data to evaluate potential roles of diet, obesity, exercise, or chemical carcinogens, and there are inconsistent reports on the role of exposure to talc, and infertility drugs, or infertility per se (Hartge et al., 1983; Cook et al., 1997; Chang et al., 1997; Glud et al., 1998; Rodriguez et al., 1998; Wong et al., 1999; Gertig et al., 2000; Venn et al., 2001). Several studies point to a role for ionizing radiation or asbestos in ovarian cancer risk (Doll and Smith, 1968; Acheson et al., 1982; Wignall and Fox, 1982; Newhouse et al.,1985; Tokuoka et al., 1987; Boice, Jr. et al., 1988).

Regarding a role for hormone replacement therapy (HRT) in ovarian cancer risk, contrary to most previous reports (Whittemore et al., 1992; Garg et al., 1998; Coughlin et al., 2000), recent case-control and cohort studies indicate that the risk of ovarian cancer is increased among ever users of hormone replacement therapy (HRT) (Rodriguez et al., 2001; Lacey et al., 2001; Riman et al., 2002).

2) Possible genetic and familial risk factors

A) Personal history of breast cancer (double primary studies):

Reports of the significantly elevated risks for multiple primary cancers originating in the ovary and the breast (Schottenfeld and Berg, 1971; Reimer et al., 1978; Prior and Waterhouse, 1981; Teppo et al., 1985) indicate that personal history of breast cancer may be a potential risk factor for ovarian cancer. The data on multiple primaries in Connecticut and Denmark indicated a significant 30-70% increased incidence of ovarian cancer following a primary cancer of the breast (Ewertz and Mouridsen, 1985; Harvey and Brinton, 1985) and a significant 40% increase in the incidence of breast cancer among women whose first primary cancer occurred in the ovary (Curtis et al., 1985). In a study evaluating genetic associations between ovarian and breast cancer, the risk of either cancer given the other was estimated to be 2.3 times the probability of the independent occurrence of each (Schildkraut et al., 1989). However, the analyses in these studies did not adjust for hormonal or reproductive risk factors. Therefore, the basis for these observed associations is not currently known. Possible explanations include the hypotheses that shared environmental, hormonal and/or genetic risk factors may be involved in the pathogenesis of both ovarian and breast cancer.

Regarding shared hormonal and reproductive risk factors, nulliparity and estrogen use are considered risk factors for both cancers (La Vecchia, 2001; Sasco, 2001). In an analysis of 12 U.S. case-control studies of ovarian cancer risk, nulliparous women had two-fold risk as compared to parous women (Whittemore et al., 1992). Similarly, excess risk of breast cancer has been reported among nulliparous women. An international collaborative case-control study by MacMahon et al. (1970) showed that the risk of breast

cancer was 40% higher among single and nulliparous married women compared to parous married women. Although previous studies reported no association between ovarian cancer risk and HRT use, recent studies indicate elevated risk (OR=1.4, 95% CI=1.0-2.0) among ever users of estrogen replacement therapy as compared with never users (Riman et al., 2002). A recent study of estrogen replacement therapy and breast cancer risk (Schairer et al., 2000) also showed increases in risk with estrogen only use (RR=1.2; 95% CI=1.0-1.4).

With regard to shared genetic risk factors, it has been reported that women with breast cancer who carry mutations in BRCA1 or BRCA2 have a ten-fold increase in the risk of subsequent ovarian cancer compared with women without mutations (Frank et al., 1998). Fishman et al. (2000) reported that the rate of BRCA1/2 mutations in Ashkenazi (of Eastern European origin) Jewish women with ovarian cancer, who had a previous primary breast cancer, was at least twice as high as in Jewish women with just ovarian cancer. In this study, women with double primary breast and ovarian cancer had a high prevalence (57%) of mutations in BRCA1 and BRCA2 genes. In addition, a recent study of the BRCA1/2 mutations in non-Ashkenazi families showed that 86% (six of seven) of women undergoing genetic testing with double primary breast and ovarian cancer were BRCA1/2 mutation carriers (Schorge et al., 2001). The presence of a woman with both ovarian and breast cancer in a breast/ovarian family is one of the strongest predictors of finding a BRCA1/2 mutation as the genetic basis for that familial cluster.

B) Familial epidemiologic studies:

Descriptive family studies--In 1929, Kimbrough noted increased concordance of ovarian cancer in twins (Kimbrough, 1929). This suggested that familial, perhaps even

genetic, factors might play a role in the development of this cancer. Further cancer family studies analyzing familial ovarian cancer pedigrees showed clustering of breast/ovarian cancer (Fraumeni, Jr. et al., 1975; Lynch et al., 1981) and extracolonic cancers including ovarian cancer with colon cancer (Watson and Lynch, 1993). In the latter study (Watson and Lynch, 1993), significant excess of ovarian cancer (O/E=3.5; P<0.001) was reported among members of the 23 high-risk families with HNPCC. It should be noted that in these "descriptive studies," the families with affected individuals comprised unusual high-risk families selected non-systematically from clinical settings. In addition, an analysis of 391 pedigrees of patients with ovarian cancer, not selected from-high risk families, showed a significant excess risk of breast cancer among first-degree relatives *older than 55 years* of patients with ovarian cancer (O/E: 1.6; 95% CI: 1.1-2.2) (Houlston et al., 1993), but not among younger relatives.

Population-based/analytic studies--A family history of ovarian cancer is considered an established risk factor for ovarian cancer (Ponder et al., 1991). In a meta-analysis of data from case-control studies, Amos et al. (1992) reported 3.6-fold increased risk of ovarian cancer among women with a first-degree relative with ovarian cancer as compared to women without affected first-degree relatives. Another report of a meta-analysis of all published case-control and cohort studies showed a significant excess risk of ovarian cancer (RR=3.1; 95% CI=2.6-3.7) among women who had first-degree relatives with ovarian cancer (Stratton et al., 1998).

In addition, there is a substantial body of evidence documenting an association between breast cancer and ovarian cancer in the same family. These studies demonstrate an excess risk of one cancer when there was a report of the other cancer in a family

member. For example, the risk of ovarian cancer was increased by 1.3-1.8-fold when there was a breast cancer in a family member (Schildkraut et al., 1989; Parazzini et al., 1992; Kerber & Slattery, 1995; Easton et al., 1996; Poole et al., 1999; Ziogas et al., 2000), and vice versa (Schildkraut et al., 1989; Thompson & Schildkraut, 1991; Peto et al., 1996; Ziogas et al., 2000).

Several epidemiologic studies (cohort and case-control) have addressed the association between ovarian cancer risk and family history of breast cancer including the number of affected relatives, and relative's age of breast cancer onset (Schildkraut and Thompson, 1988; Schildkraut et al., 1989; Easton et al., 1996; Ziogas et al., 2000). For example, a recent population-based breast and ovarian cancer study showed an increasing trend in the risk of ovarian cancer risk with increasing number of affected first-degree relatives with breast cancer (test for trend, $p = 0.0002$) (Ziogas et al., 2000). Schildkraut and Thompson (1988) showed that women with ovarian cancer were more likely than controls to report a relative with age of onset of breast cancer prior to age 55 years (OR: 1.9; 95% CI: 1.2-3.0). However, the result from this population-based case-control study was contrary to what was reported from an analysis of 391 pedigrees of patients with ovarian cancer (Houlston et al., 1993). A study of breast cancer mortality in mothers and sisters of women with ovarian cancer showed non-significant excesses of mortality for age groups of <40 (O/E: 4/1.45), 50-59 (O/E: 21/12.9), and 70-79 (O/E: 12/9.6) years old (Easton et al. 1996). Schildkraut et al. (1989) reported that ovarian cancer probands with later age at onset (>45) showed increased risk (RR: 3.1; CI: 1.7-5.7) of early age ($\leq$45) at onset of breast cancer in their relatives (mothers and sisters). However, no studies have looked at the risk of ovarian cancer as it may relate to the laterality of breast cancer in

family members. These variables are of interest because they are felt to represent clinical clues to the presence of a hereditary cancer predisposition.

C) Genetic studies:

The hereditary breast/ovarian cancer syndrome (HBOC) is an important genetic disorder that predisposes to both ovarian and breast cancer. Segregation analysis of 18 large families provided evidence for the association of breast and ovarian cancer resulting from a common genetic etiology (Go et al., 1983). Inherited mutations in the genes BRCA1 and BRCA2 are responsible for most (80-90%) hereditary ovarian cancers (Miki et al., 1994; Narod et al., 1995; Tavtigian et al., 1996; Boyd, 1998) as well as the majority of hereditary breast cancers (i.e., families with at least four cases of either female breast cancer diagnosed at age <60 years or male breast cancer diagnosed at any age) (Ford et al., 1998). This implies that the majority of hereditary ovarian cancers occur in the setting of familial breast cancer (Prior and Waterhouse, 1981). This disorder has been designated HBOC.

More than half a million American women are estimated to be carriers of a mutation in one of the breast cancer susceptibility genes, BRCA1 or BRCA2 (Ziogas et al., 2000). The frequency of mutations in the general population is estimated to be about 1 in 800 for BRCA1 and somewhat less for BRCA2 and this can vary significantly by ethnicity (Ford et al., 1995; Struewing et al., 1995; Szabo and King, 1997; Berchuck et al., 1999; Antoniou et al., 2000). These mutations are usually unique to a single family (Shattuck-Eidens et al., 1995). On the other hand, recurrent mutations or "founder mutations" (arising from common ancestry) have been identified in almost all populations studied, e.g., Icelandic (Thoralicus et al., 1997), Swedish (Hakansson et al.,

1997), Spanish (Diez et al., 1999), French Canadian (Tonin et al., 1998), Chinese (Khoo et al., 1999), and Ashkenazi Jewish (Struewing et al., 1995; Levy-Lahad et al., 1997; Moslehi et al., 2000).

Jewish ancestry as it relates to the high incidence (2.5% of both genders) of mutations in BRCA1 and BRCA2 is considered an established risk factor for ovarian cancer (FitzGerald et al., 1996; Abeliovich et al., 1997; Beller et al., 1997; Struewing et al., 1995; Oddoux et al., 1996; Roa et al., 1996). In Ashkenazi Jewish populations, three recurrent mutations have been identified (Fitzgerald et al., 1996; Offit et al., 1996; Simard et al., 1994; Tonin et al., 1995; Friedman et al., 1994; Neuhausen et al., 1995). These founder mutations are BRCA1 185delAG (exon 2) (Streuwing et al., 1995; Fitzgerald et al., 1996; Tonin et al., 1995; Roa et al., 1996), BRCA1 5382insC (exon 20) (Shattuck-Eidens et al., 1995; Simard et al., 1994; Neuhausen et al., 1995), and BRCA2 6174delT (Oddoux et al., 1996), which are present at a frequency of 1.1% , 0.1%, and 1.4%, respectively.

It has been reported that the age-specific risk of ovarian cancer in carriers of these genes are 15 times higher than that in non-carriers (Claus et al., 1996). It is currently believed that loss of the DNA repair function of the encoded proteins by mutated BRCA1 and BRCA2 genes results in carcinogenesis, perhaps because of accumulation of un-repaired somatic mutations. The lifetime risk of breast and ovarian cancer in female carriers of BRCA1 mutations is estimated to be approximately 50%-85% and 15-45%, respectively (Gayther et al., 1997; Lynch et al., 1999). Women who carry BRCA1 mutations also have an increased incidence of bilateral breast cancer, with a second primary breast cancer occurring in 40% to 60% of patients (Lynch et al., 1999). It has

been estimated that the BRCA2 gene is responsible for a smaller proportion of hereditary breast and ovarian cancer cases (Wooster et al., 1994). The carriers of mutations in this gene are at lower risk of ovarian cancer (i.e., lower "penetrance") than that which is seen with BRCA1 mutations (Wooster et al., 1995). The lifetime risk of breast and ovarian cancer in BRCA2 mutation carriers are 50%-85% and 10-20%, respectively (Lynch et al., 1999; Hopper et al., 1999). The preceding penetrance estimates were derived from the study of highly selected, dramatically affected breast/ovarian cancer families that were used to map and clone the BRCA genes. Concern that this methodology may have yielded over-estimates of penetrance was borne out when data became available from populations that were closer to general population samples, such as the Washington Ashkenazi Study and other general breast cancer populations (Struewing et al., 1997; Couch et al., 1997; Krainer et al., 1997; Healy, 1997). In the study by Struewing et al. (1997), for example, the estimated risk of breast and ovarian cancer among carriers of BRCA1 and BRCA2 genes were 56% and 16%, respectively. The penetrance of BRCA-associated ovarian cancer in these studies was lower than what was reported in the very high-risk families reported by the Breast Cancer Linkage Consortium.

It has also been hypothesized that there might be a distinct clinical syndrome of pure, site-specific ovarian cancer based on the reports of families with multiple cases of ovarian cancer and no obvious excess of breast cancer (Narod et al., 1994; Lynch et al., 1991a,b; Bewtra et al., 1992; Liede et al., 1998). However, genetic linkage analysis and germline mutation testing has demonstrated that all of these families are associated with mutations in the breast and ovarian cancer susceptibility gene BRCA1 (Steichen-Gersdorf et al., 1994; Boyd and Rubin, 1997), suggesting that these families belong to the breast

and ovarian cancer syndrome families in which early-onset breast cancer has not yet appeared. Alternatively, this pattern may reflect specific genotype/phenotype relationships in BRCA1/2, in which mutations located in a specific region of one of these genes may be much more likely to result in ovarian cancer than mutations elsewhere in the same gene. A new report of genotype/phenotype correlations among affected families with BRCA1 mutations showed that the ovarian:breast cancer ratio associated with mutations in a central region of the gene (nucleotides 2401-4190) was significantly higher than with other mutations (nucleotides 1-2400 and 4191-end) (Thompson and Easton, 2002). Similarly, the data for this phenomenon for BRCA2 suggests that mutations in a specific region of the gene known as the "ovarian cancer cluster region" were associated with a significantly higher ratio of cases of ovarian:breast cancer than were mutations in other regions (i.e., 5' or 3' of this region) (Thompson and Easton, 2001).

Ovarian cancer is also one of the extra-colonic malignancies that occurs excessively in persons with hereditary nonpolyposis colorectal cancer (HNPCC) (Bewtra et al., 1992; Watson and Lynch, 1993). Approximately 2% of hereditary ovarian cancer cases occur in the context of HNPCC syndrome (Lynch et al., 1991c; Lynch et al., 1998; Lengauer et al., 1997). It has been reported that more than 90% of all reported mutations in HNPCC kindreds involve germline mutations in one or the other of two DNA mismatch repair genes, hMSH2 or hMLH1 (Boyd and Rubin, 1997). Vasen et al. (1996) reported that the carriers of hMSH2 mutations had a significant eight-fold excess risk of ovarian cancer. The estimated risk of ovarian cancer to age 70 in women with mutations in one of the mismatch repair genes is approximately 9% (Aarnio et al., 1995), compared with 1.4% in

the general population (Parkin et al., 1997). It has been suggested by some (but not all) investigators that HNPCC may also include a predisposition to breast cancers (Risinger et al., 1996; Scott et al., 2001) among members of the same family. The cumulative risk of breast cancer in these families is not well defined, and it is currently controversial as to whether breast cancer truly is one of the extra-colonic malignancies that is part of the HNPCC disease spectrum.

SUMMARY

Reports of families with endometrial cancer and breast cancer, or ovarian cancer and breast cancer, and double primary cancers (both in multiple case families and sporadic individuals), suggest a common, and possibly genetic etiology for these cancers. Although descriptive family studies reporting clustering of ovarian and breast cancer in the same families, and several epidemiologic studies indicate an association between some ovarian and breast cancers, this relationship has not been well established at the general population level. A possible genetic link between endometrial and breast cancer has been less well studied. The available literature is inconsistent with regard to family history of any cancer in the development of endometrial cancer. In addition, lifetime risk of endometrial cancer and breast cancer in Cowden's syndrome and HNPCC, respectively, are not clearly defined.

To investigate further the hypothesis that family history of breast cancer may increase the risk of developing endometrial or ovarian cancer in the general population setting, I analyzed data from Breast Cancer Detection Demonstration Project (BCDDP)

Follow-up Study (Schairer et al., 2000). This study included detailed information regarding the number and relationship of relatives affected with breast cancer, their age at breast cancer diagnosis, and breast cancer laterality. Because early age at breast cancer diagnosis, bilateral disease and multiple relatives with breast cancer are hallmarks of a genetic association, the information available from this study might provide important clues as to whether associations between endometrial cancer and ovarian cancer with breast cancer are due to shared genetic and/or environmental factors.

This study is unique in that detailed family history information including the aforementioned features and the information on other risk factors were periodically updated throughout the study. These data allow a more accurate estimate of the rate ratios through time-dependent analyses, in which the exposure status classification of study participants is determined over time

REFERENCES

Aarnio M, Mecklin JP, Aaltonen LA, Nystrom-Lahti M, Jarvinen HJ. Lifetime risk of different cancers in hereditary non-polyposis colorectal cancer (HNPCC) syndrome. Int J Cancer 1995; 64:430-3.

Aarnio M, Sankila R, Pukkala E, Salovaara R, Aaltonen LA, de la Chapelle A, Peltomaki P, Mecklin JP, Jarvinen HJ. Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer 1999; 81:214-8.

Abeliovich D, Kaduri L, Lerer I, Weinberg N, Amir G, Sagi M, Zlotogora J, Heching N, Peretz T. The founder mutations 185delAG and 5382insC in BRCA1 and 6174delT in BRCA2 appear in 60% of ovarian cancer and 30% of early-onset breast cancer patients among Ashkenazi women. Am J Hum Genet 1997; 60:505-14.

Acheson ED et al (1982) Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. Br J Ind Med 1982; 39:344-348.

Altchek A, Deligdisch L. Diagnosis and management of ovarian disorders. Igaku-Shoin, New York, Tokyo 1996.

American Cancer Society. Cancer Facts & Figures. American Cancer Society, Inc. Atlanta, GA. 2002.

Amos CI, Struewing JP. Genetic epidemiology of epithelial ovarian cancer. Cancer 1993; 71:566-72.

Anderson D.E., and Badzioch M.D. Familial breast cancer risks. Cancer 1993; 72:114-9.

Antoniou AC, Gayther SA, Stratton JF, Ponder BA, Easton DF. Risk models for familial ovarian and breast cancer. Genet Epidemiol. 2000;18:173-90.

Assikis VJ, Jordan VC Gynecologic effects of tamoxifen and the association with endometrial carcinoma. Int J Gynaecol Obstet 1995; 49:241-257.

Bandera CA, Boyd J. The molecular genetics of endometrial carcinoma. Prog Clin Biol Res 1997; 396:185-203.

Barakat RR Endometrial cancer and tamoxifen. Primary Care & Cancer 1999; 19 (Suppl. 1):27-30 .

Beller U, Halle D, Catane R, Kaufman B, Hornreich G, Levy-Lahad E. High frequency of BRCA1 and BRCA2 germline mutations in Ashkenazi Jewish ovarian cancer patients, regardless of family history. Gynecol Oncol 1997; 67:123-6.

Berchuck A, Schildkraut JM, Marks JR, Futreal PA. Managing hereditary ovarian cancer risk. Cancer 1999; 86:2517-24.

Bertelli, G, Pronzato P, Amoroso D, et al. Adjuvant tamoxifen in primary breast cancer: influence on plasma lipids and antithrombin III levels. Breast Cancer Res Treat 1988; 12:307-310.

Bernstein L, Deapen D, Cerhan JR, et al. Tamoxifen therapy for breast cancer and endometrial cancer risk. J Natl Cancer Inst 1999; 91:1654-1662.

Bewtra C, Watson P, Conway T, Read-Hippee C, Lynch HT. Hereditary ovarian cancer: a clinicopathological study. Int J Gynecol Pathol 1992; 11:180-7.

Boice JD Jr, Engholm G, Kleinerman RA, Blettner M, Stovall M, Lisco H, Moloney WC, Austin DF, Bosch A, Cookfair DL, et al.Radiation dose and second cancer risk in patients treated for cancer of the cervix. Radiat Res 1988; 116:3-55.

Boltenberg A, Furgyik S, Kullander S. Familial cancer aggregation in cases of adenocarcinoma corporis uteri. Acta Obstet Gynecol Scand 1990; 69:249-58.

Boring CC, Squires TS, Tong T, Montgomery S. Cancer statistics 1994. CA Cancer J Clin 1994; 44:7-26.

Boyd J. Estrogen as a carcinogen: the genetics and molecular biology of human endometrial carcinoma. Prog Clin Biol Res 1996; 394:151-73.

Boyd J and Rubin SC. Hereditary ovarian cancer: molecular genetics and clinical implications. Gynecol Oncol 1997; 64:196-206.

Boyd J. Molecular genetics of hereditary ovarian cancer. Oncology (Huntingt) 1998;12:399-406.

Brinton LA, Hoover RN. Epidemiology of gynecologic cancers. In: Hoskins W.J., Perez C.A., Young R.C., editors. Principles and practice of gynecologic oncology. Philadelphia: Lipincott 3-26, 1992.

Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD, Lannom L, Hoover RN. Reproductive, menstrual, and medical risk factors for endometrial cancer: results from a case-control study. Am J Obstet Gynecol 1992; 167:1317-25.

Brinton LA, Barrett RJ, Berman ML, Mortel R, Twiggs LB, Wilbanks GD. Cigarette smoking and the risk of endometrial cancer. Am J Epidemiol 1993; 137:281-91.

Bruning PF, Bonfrer JM, Hart AA, et al. Tamoxifen, serum lipoproteins and cardiovascular risk. Br J Cancer 1988; 58:497-499.

Chang S and Risch HA. Perineal talc exposure and risk of ovarian carcinoma. Cancer 1997; 79:2396-2401.

Claus EB, Schildkraut JM, Thompson WD, Risch NJ. The genetic attributable risk of breast and ovarian cancer. Cancer 1996; 77:2318-24.

Cook LS, Kamb ML, and Weiss NS. Perineal powder exposure and the risk of ovarian cancer. Am J Epidemiol 1997; 145:459-465.

Couch FJ, DeShano ML, Blackwood MA, Calzone K, Stopfer J, Campeau L, Ganguly A, Rebbeck T, Weber BL. BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. N Engl J Med 1997; 336:1409-15.

Coughlin SS, Giustozzi A, Smith SJ, Lee NC. A meta-analysis of estrogen replacement therapy and risk of epithelial ovarian cancer. J Clin Epidemiol 2000; 53:367-375.

Curtis RE, Hoover RN, Kleinerman RA, Harvey EB. Second cancer following cancer of the female genital system in Connecticut, 1935-82. Natl Cancer Inst Monogr 1985; 68:113-37.

Deligdisch L, Holinka CF. Endometrial carcinoma: two diseases? Cancer Detect Prev 1987; 10:237-46.

Diez O, Osorio A, Robledo M, Barroso A, Domenech M, Cortes J, Albertos J, Sanz J, Brunet J, SanRoman JM, Alonso MC, Baiget M, Benitez J. Prevalence of BRCA1 and BRCA2 Jewish mutations in Spanish breast cancer patients. Br J Cancer 1999; 79:1302-3.

Doll R and Smith PG. The long-term effects of x irradiation in patients treated for metropathia haemorrhagica. Br J Radiol 1968; 41:362-368.

Easton DF, Matthews FE, Ford D, Swerdlow AJ, Peto J. Cancer mortality in relatives of women with ovarian cancer: the OPCS Study. Office of Population Censuses and Surveys. Int J Cancer 1996; 65:284-94.

Elwood JM, Cole P, Rothman KJ, Kaplan SD. Epidemiology of endometrial cancer. British Journal of Hospital Medicine 1997; 59:1055-1060.

Eng C. Genetics of Cowden syndrome: through the looking glass of oncology. Int J Oncol 1998; 12:701-10.

Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. J Med Genet 2000; 37:828-30.

Ewertz M and Mouridsen HT. Second cancer following cancer of the female breast in Denmark, 1943-80. Natl Cancer Inst Monogr 1985; 68:325-9.

Fishel R, Lescoe M.K., Rao M.R.S. et al. The human mutator gene homolog MSH2 and its association with hereditary nonpolyposis colon cancer. Cell 1993; 75:1027-1038.

Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. J Natl Cancer Inst 1994; 86:527-37.

Fishman A, Dekel E, Chetrit A, Lerner-Geva L, Bar-Am A, Beck D, Beller U, Ben-Baruch G, Piura B, Friedman E, Struewing JP, Modan B. Patients with double primary tumors in the breast and ovary- clinical characteristics and BRCA1-2 mutations status. Gynecol Oncol; 2000: 79:74-8.

FitzGerald MG, MacDonald DJ, Krainer M, Hoover I, O'Neil E, Unsal H, Silva-Arrieto S, Finkelstein DM, Beer-Romero P, Englert C, Sgroi DC, Smith BL, Younger JW, Garber JE, Duda RB, Mayzel KA, Isselbacher KJ, Friend SH, Haber DA. Germ-line BRCA1 mutations in Jewish and non-Jewish women with early-onset breast cancer. N Engl J Med 1996; 334:143-9.

Ford D., Easton DF, Peto J. Estimates of the gene frequency of BRCA1 and its contribution to breast and ovarian cancer incidence. Am J Hum Genet 1995; 57:1457-62.

Ford D, Easton DF, Stratton M, et al: Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet 1998; 62:676-89.

Fornander T, Rutqvist LE, Cedermark B, et al. Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. Lancet 1989; 1:117-120.

Fox H. Malignant potential of benign ovarian cysts: The case "against." In: Sharp F, mason WP, Leake RE, eds. Ovarian Cancer. London: Chapman and Hall, 1990;185-186.

Frank TS, Manley SA, Olopade OI, Cummings S, Garber JE, Bernhardt B, Antman K, Russo D, Wood ME, Mullineau L, Isaacs C, Peshkin B, Buys S, Venne V, Rowley PT, Loader S, Offit K, Robson M, Hampel H, Brener D, Winer EP, Clark S, Weber B, Strong LC, Thomas A, et al. Sequence analysis of BRCA1 and BRCA2: correlation of mutations with family history and ovarian cancer risk. J Clin Oncol 1998; 16:2417-25.

Fraumeni JF Jr, Grundy GW, Creagan ET, Everson RB. Six families prone to ovarian cancer. Cancer 1975; 36:364-9.

Friedman LS, Szabo CI, Ostermeyer EA, Dowd P, Butler L, Park T, Lee MK, Goode EL, Rowell SE, King MC. Novel inherited mutations and variable expressivity of BRCA1

alleles, including the founder mutation 185delAG in Ashkenazi Jewish families. Am J Hum Genet 1995; 57:1284-97.

Garg PP, Kerlikowske K, Subak L, Grady D. Hormone replacement therapy and the risk of epithelial ovarian carcinoma: a meta-analysis. Obstet Gynecol 1998; 92:472-479.

Garzo VG, Dorrington JH. Aromatase activity in human granulosa cells during follicular development and the modulation by follicle-stimulating hormone and insulin. Am J Obstet Gynecol 1984; 148:657-62.

Gayther SA, Ponder BA. Mutations of the BRCA1 and BRCA2 genes and the possibilities for predictive testing. Mol Med Today 1997; 3:168-74.

Gertig DM, Hunter DJ, Cramer DW, Colditz GA, Speizer FE, Willett WC, Hankinson SE.Prospective study of talc use and ovarian cancer. J Natl Cancer Inst 2000; 92:249-252.

Glud E, Kjaer SK, Troisi R, Brinton LA.Fertility drugs and ovarian cancer. Epidemiol Rev 1998; 20:237-257.

Go RC, King MC, Bailey-Wilson J, Elston RC, Lynch HT. Genetic epidemiology of breast cancer and associated cancers in high-risk families. I. Segregation analysis. J Natl Cancer Inst 1983; 71:455-61.

Gottardis MM, Robinson SP, Satyaswaroop PG, Jordan VC. Contrasting actions of tamoxifen on endometrial and breast tumor growth in the athymic mouse. Cancer Res 1988; 48:812-815.

Gradishar WJ, Jordan VC. Clinical potential of new antiestrogens. J Clin Oncol 1997; 15:840-852.

Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. Obstet Gynecol 1995; 85:304-13.

Gruber SB, Thompson WD. A population-based study of endometrial cancer and familial risk in younger women. Cancer and Steroid Hormone Study Group. Cancer Epidemiol Biomarkers Prev 1996; 5:411-417.

Hakala T, Mecklin JP, Forss M, Jarvinen H, Lehtovirta P. Endometrial carcinoma in the cancer family syndrome. Cancer 1991; 68:1656-9.

Hakansson S, Johannsson O, Johansson U, Sellberg G, Loman N, Gerdes AM, Holmberg E, Dahl N, Pandis N, Kristoffersson U, Olsson H, Borg A. Moderate frequency of BRCA1 and BRCA2 germ-line mutations in Scandinavian familial breast cancer. Am J Hum Genet 1997; 60:1068-78.

Hankinson SE, Hunter DJ, Colditz GA, Willett WC, Stampfer MJ, Rosner B, Hennekens CH, Speizer FE.Tubal ligation, hysterectomy, and risk of ovarian cancer. A prospective study. JAMA 1993; 270:2813-2818.

Harvey E.B., Brinton L.A., Second cancer following cancer of the breast in Connecticut. 1935-1982. Natl Cancer Inst Monogr 1985; 68: 99-112.

Hartge P, Hoover R, Lesher LP, McGowan L. Talc and ovarian cancer. JAMA 1983; 250:1844.

Hopper JL, Southey MC, Dite GS, Jolley DJ, Giles GG, McCredie MR, Easton DF, Venter DJ. Population-based estimate of the average age-specific cumulative risk of breast cancer for a defined set of protein-truncating mutations in BRCA1 and BRCA2. Australian Breast Cancer Family Study. Cancer Epidemiol Biomarkers Prev 1999; 8:741-7.

Howell, A. Antiestrogens: future prospects. Oncology 1997; 11 (Suppl. 1):59-64.

Healy B. BRCA genes--bookmaking, fortunetelling, and medical care. N Engl J Med 1997; 336:1448-1449.

Henderson BE, Casagrande JT, Pike MC, Mack T, Rosario I, Duke A. The epidemiology of endometrial cancer in young women. Br J Cancer 1983; 47:749-56.

Houlston RS, Bourne TH, Collins WP, Whitehead MI, Campbell S, Slack J. Risk of ovarian cancer and genetic relationship to other cancers in families. Hum Hered 1993; 43:111-5.

Hoover R, Fraumeni JF, Everson R, Myers MH. Cancer of the uterine corpus after hormonal treatment for breast cancer. Lancet 1976; 1:885-7.

Jass J.R., Stewart S.M., Schroeder D. et al. Screening for hereditary nonpolyposis colorectal cancer in New Zealand. Eur J Gastroenterol Hepatol 1992; 4:523-527.

Kaaks R. Nutrition, hormones, and breast cancer: is insulin the missing link? Cancer Causes Control 1996; 7:605-25.

Kauffman, RF, Bryant HU Selective estrogen receptor modulators. Drug News and Perspectives 1995; 8:531-539.

Kelsey JL, LiVolsi VA, Holford TR, Fischer DB, Mostow ED, Schwartz PE, O'Connor T, White C. A case-control study of cancer of the endometrium. Am J Epidemiol 1982; 116:333-42.

Kerber RA, Slattery ML. The impact of family history on ovarian cancer risk. The Utah Population Database. Arch Intern Med 1995; 155:905-12.

Key TJ, Pike MC. The dose-effect relationship between 'unopposed' oestrogens and endometrial mitotic rate: its central role in explaining and predicting endometrial cancer risk. Br J Cancer 1988; 57:205-12.

Khoo US, Ozcelik H, Cheung AN, Chow LW, Ngan HY, Done SJ, Liang AC, Chan VW, Au GK, Ng WF, Poon CS, Leung YF, Loong F, Ip P, Chan GS, Andrulis IL, Lu J, Ho FC. Somatic mutations in the BRCA1 gene in Chinese sporadic breast and ovarian cancer. Oncogene 1999; 18:4643-6.

Kimbrough RA. Coincident carcinoma of the ovary in twins. Am J Obstet Gynecol 1929; 18:148-149.

Krainer M, Silva-Arrieta S, FitzGerald MG, Shimada A, Ishioka C, Kanamaru R, MacDonald DJ, Unsal H, Finkelstein DM, Bowcock A, Isselbacher KJ, Haber DA. Differential contributions of BRCA1 and BRCA2 to early-onset breast cancer. N Engl J Med 1997; 336:1416-21.

Ku J.L., Yoon K.A., Kim D.Y.,Park J.G.. Mutations in hMSH6 alone are not sufficient to cause the microsatellite instability in colorectal cancer cell lines. Eur J Cancer 1999; 35: 1724-9.

Kurman RJ, Norris HJ. Endometrial carcinoma. In Kurman RJ (eds): Blaustein's Pathology of the Female Genital Tract. New York: Springer-Verlag 1987:338-372.

Kuschel B, Lux MP, Goecke TO, Beckmann MW. Prevention and therapy for BRCA1/2 mutation carriers and women at high risk for breast and ovarian cancer. Eur J Cancer Prev 2000; 9:139-50.

Lacey JV, Mink PJ, Lubin JH, Sherman ME, Troisi R, Hartge P, Schatzkin A, Schairer C. Menopausal hormone replacement therapy and risk of ovarian cancer in a prospective study. Submitted to JAMA, 2001.

La Vecchia C. Epidemiology of ovarian cancer: a summary review. Eur J Cancer Prev. 2001; 10:125-9.

Leach FS, Nicolaides NC, Papadopoulos N. et al. Mutations of a mutS homolog in hereditary nonpolyposis colorectal cancer. Cell 1993; 75:1215-1225.

Lengauer C, Kinzler KW, Vogelstein B. Genetic instability in colorectal cancers. Nature 1997; 386:623-7.

Levy-Lahad E, Catane R, Eisenberg S, Kaufman B, Hornreich G, Lishinsky E, Shohat M, Weber BL, Beller U, Lahad A, Halle D. Founder BRCA1 and BRCA2 mutations in Ashkenazi Jews in Israel: frequency and differential penetrance in ovarian cancer and in breast-ovarian cancer families. Am J Hum Genet 1997; 60:1059-67.

Love RR, Newcomb PA, Wiebe DA, et al. Effects of tamoxifen therapy on lipid and lipoprotein levels in postmenopausal patients with node-negative breast cancer. J Natl Cancer Inst 1990; 82:1327-1332.

Love RR, Mazess RB, Barden HS, et al. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. N Engl J Med 1992; 326:852-856.

Liaw D, Marsh DJ, Li J, Dahia PL, Wang SI, Zheng Z, Bose S, Call KM, Tsou HC, Peacocke M, Eng C, Parsons R. Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. Nat Genet 1997; 16:64-7.

Liede A, Tonin PN, Sun CC, Serruya C, Daly MB, Narod SA, Foulkes WD. Is hereditary site-specific ovarian cancer a distinct genetic condition? Am J Med Genet 1998; 75:55-8.

Lynch H.T., Shaw M.W., Magnuson C.W., Larsen A. L., Krush, A. J. Hereditary factors in cancer: study of two large Midwestern kindred. Arch Intern Med 1966; 117: 206-212.

Lynch H.T., Krush A.J. Heredity and adenocarcinoma of the colon. Gastroenterology 1967; 53: 517-527.

Lynch HT, Krush AJ, Lemon HM, Kaplan AR, Condit PT, Bottomley RH. Tumor variation in families with breast cancer. JAMA 1972; 222:1631-5.

Lynch HT, Albano W, Black L, Lynch JF, Recabaren J, Pierson R. Familial excess of cancer of the ovary and other anatomic sites. JAMA 1981; 245:261-4.

Lynch HT, Conway T, and Lynch J. Hereditary ovarian cancer. Pedigree studies, Part II. Cancer Genet Cytogenet 1991a; 53:161-183.

Lynch HT, Watson P, Bewtra C, Conway TA, Hippee CR, Kaur P, Lynch JF, Ponder BA. Hereditary ovarian cancer. Heterogeneity in age at diagnosis. Cancer 1991b; 67:1460-6.

Lynch HT, Lynch JF. Familial factors and genetic predisposition to cancer: population studies. Cancer Detect Prev 1991c; 15:49-57.

Lynch HT, Lynch J, Conway T, Watson P, Coleman RL. Familial aggregation of carcinoma of the endometrium. Am J Obstet Gynecol 1994; 171:24-7.

Lynch HT, Casey MJ, Lynch J, White TE, Godwin AK. Genetics and ovarian carcinoma. Semin Oncol 1998; 25:265-80.

Lynch HT, Watson P, Tinley S, Snyder C, Durham C, Lynch J, Kirnarsky Y, Serova O, Lenoir G, Lerman C, Narod SA. An update on DNA-based BRCA1/BRCA2 genetic counseling in hereditary breast cancer. Cancer Genet Cytogenet 1999; 109:91-8.

Lyon FA. The development of adenocarcinoma of the endometrium in young women receiving long-term sequential oral contraception. Am J Obstet Gynecol 1975; 123:299-301.

MacMahon B, Cole P, Lin TM, Lowe CR, Mirra AP, Ravnihar B, Salber EJ, Valaoras VG, Yuasa S. Age at first birth and breast cancer risk. Bull World Health Organ 1970; 43:209-21.

MacMahon B. Risk factors for endometrial cancer. Gynecol Oncol 1974; 2:122-9.

Marsh D.J., Coulon V., Lunetta K.L., Rocca-Serra P., Dahia P.L., Zheng Z., Liaw D., Caron S., Duboue B., Lin A.Y., Richardson A.L., Bonnetblanc J.M., Bressieux J.M., Cabarrot-Moreau A., Chompret A., Demange L., Eeles R.A., Yahanda A.M., Fearon E.R., Fricker J.P., Gorlin R.J., Hodgson S.V., Huson S., Lacombe D., Eng C., et al. Mutation spectrum and genotype-phenotype analyses in Cowden disease and Bannayan-Zonana syndrome, two hamartoma syndromes with germline PTEN mutation. Hum Mol Genet 1998; 7:507-15.

McDonald TW, Malkasian GD, Gaffey TA. Endometrial cancer associated with feminizing ovarian tumor and polycystic ovarian disease. Obstet Gynecol 1977; 49:654-8.

Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994; 266:66-71.

Mink PJ, Folsom AR, Sellers TA, Kushi LH. Physical activity, waist-to-hip ratio, and other risk factors for ovarian cancer: a follow-up study of older women. Epidemiology 1996; 7:38-45.

Mori M, Harabuchi I, Miyake H, Casagrande JT, Henderson BE, Ross RK. Reproductive, genetic, and dietary risk factors for ovarian cancer. Am J Epidemiol 1988; 128:771-777.

Moslehi R, Chu W, Karlan B, Fishman D, Risch H, Fields A, Smotkin D, Ben-David Y, Rosenblatt J, Russo D, Schwartz P, Tung N, Warner E, Rosen B, Friedman J, Brunet JS,

Narod SA. BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer. Am J Hum Genet 2000; 66:1259-72.

Muto MG, Cramer DW, Tangir J, Berkowitz R, Mok S. Frequency of the BRCA1 185delAG mutation among Jewish women with ovarian cancer and matched population controls. Cancer Res 1996; 56:1250-2.

Mutter GL, Lin MC, Fitzgerald JT, Kum JB, Baak JP, Lees JA, Weng LP, Eng C. Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. J Natl Cancer Inst 2000; 92:924-30.

Narod SA, Madlensky L, Bradley L, Cole D, Tonin P, Rosen B, Risch HA. Hereditary and familial ovarian cancer in southern Ontario. Cancer 1994; 74:2341-6.

Narod SA, Ford D, Devilee P, Barkardottir RB, Lynch HT, Smith SA, Ponder BA, Weber BL, Garber JE, Birch JM, et al. An evaluation of genetic heterogeneity in 145 breast-ovarian cancer families. Breast Cancer Linkage Consortium. Am J Hum Genet 1995; 56:254-64.

Narod SA. Hormonal prevention of hereditary breast cancer. Ann N Y Acad Sci 2001; 952:36-43.

National Cancer Institute. Ovarian Epithelial Cancer. http://cancernet.nci.nih.gov/clinpdq/soa/Ovarian_epithelial_cancer_Physician.html. 1999

Neuhausen SL, Mazoyer S, Friedman L, Stratton M, Offit K, Caligo A, Tomlinson G, Cannon-Albright L, Bishop T, Kelsell D, Solomon E, Weber B, Couch F, Struewing J, Tonin P, Durocher F, Narod S, Skolnick MH, Lenoir G, Serova O, Ponder B, Stoppa-Lyonnet D, Easton D, King MC, Goldgar DE. Haplotype and phenotype analysis of six recurrent BRCA1 mutations in 61 families: results of an international study. Am J Hum Genet 1996; 58:271-80.

Nelson CL, Sellers TA, Rich SS, Potter JD, McGovern PG, Kasha LH. Familial clustering of colon, breast, uterine, and ovarian cancers as assessed by family history. Genet Epidemiol 1993; 10:235-244.

Nestler JE, Powers LP, Matt DW, Steingold KA, Plymate SR, Rittmaster RS, Clore JN,Blackard WG. A direct effect of hyperinsulinemia on serum sex hormone-binding globulin levels in obese women with the polycystic ovary syndrome. J Clin Endocrinol Metab 1991; 72:83-9.

Newhouse ML, Berry G, and Wagner JC. Mortality of factory workers in east London 1933-80. Br J Ind Med 1985; 42:4-11.

Nicolaides NC, Papadopoulos N, Liu B et al. Mutations of two PMS homologues in hereditary nonpolyposis colon cancer. Nature 1994; 371:75-80.

Oddoux C, Struewing JP, Clayton CM, Neuhausen S, Brody LC, Kaback M, Haas B, Norton L, Borgen P, Jhanwar S, Goldgar D, Ostrer H, Offit K. The carrier frequency of the BRCA2 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%. Nat Genet 1996; 14:188-90.

Offit K, Gilewski T, McGuire P, Schluger A, Hampel H, Brown K, Swensen J, Neuhausen S, Skolnick M, Norton L, Goldgar D. Germline BRCA1 185delAG mutations in Jewish women with breast cancer. Lancet 1996; 347:1643-5.

Olson JE, Sellers TA, Anderson KE, Folsom AR. Does a family history of cancer increase the risk for postmenopausal endometrial carcinoma? A prospective cohort study and a nested case-control family study of older women. Cancer 1999a; 85:2444-2449.

Olsen JH, Seersholm N, Boice JD Jr, Kruger Kjaer S, Fraumeni JF Jr.
Cancer risk in close relatives of women with early-onset breast cancer--a population-based incidence study. Br J Cancer 1999; 79:673-9.

Osborne CK. Tamoxifen in the treatment of breast cancer. New Engl J Med 1998; 339:1609-1618.

Parazzini F, La Vecchia C, Bocciolone L, Franceschi S. The epidemiology of endometrial cancer. Gynecol Oncol 1991; 41:1-16.

Parazzini F, Negri E, La Vecchia C, Restelli C, Franceschi S. Family history of reproductive cancers and ovarian cancer risk: an Italian case-control study. Am J Epidemiol 1992; 135:35-40.

Parazzini F, La Vecchia C, Negri E, Franceschi S, Tozzi L. Family history of breast, ovarian and endometrial cancer and risk of breast cancer. Int J Epidemiol 1993; 22:614-618.

Parazzini F, La Vecchia C, Moroni S, Chatenoud L, Ricci E. Family history and the risk of endometrial cancer. Int J Cancer 1994; 59:460-2.

Parazzini F, La Vecchia C, Negri E, Riboldi GL, Surace M, Benzi G, Maina A, Chiaffarino F. Diabetes and endometrial cancer: an Italian case-control study. Int J Cancer 1999; 81:539-42.

Parkin D, Muir C, Whelan SL, Ferlay J, Raymond L, Young J. Cancer Incidence in Five Continents. IARC Scientific Publications 1997; VII:1018-9.

Parslov M, Lidegaard O, Klintorp S, Pedersen B, Jonsson L, Eriksen PS, Ottesen B. Risk factors among young women with endometrial cancer: a Danish case-control study. Am J Obstet Gynecol 2000; 182:23-9.

Plaschke J., Kruppa C., Tischler R., Bocker T., Pistorius S., Dralle H., Ruschoff J., Saeger H.D., Fishel R., Schackert H,K. Sequence analysis of the mismatch repair gene

hMSH6 in the germline of patients with familial and sporadic colorectal cancer. Int J Cancer 2000;85:606-13.

Ponder BAJ, Easton DF, Peto J. Risk of ovarian cancer associated with a family history: Preliminary report of the OPCS study. In: Sahrp F, et al., eds. Ovarian Cancer: Biological and Therapeutic Challenges. New York: W.W. Norton, pp.3-6.

Poole CA, Byers T, Calle EE, Bondy J, Fain P, Rodriguez C. Influence of a family history of cancer within and across multiple sites on patterns of cancer mortality risk for women. Am J Epidemiol 1999; 149:454-62.

Poretsky L, Kalin MF. The gonadotropic function of insulin. Endocr Rev 1987; 8:132-41.

Peto J, Easton DF, Matthews FE, Ford D, Swerdlow AJ. Cancer mortality in relatives of women with breast cancer: the OPCS Study. Office of Population Censuses and Surveys. Int J Cancer 1996; 65:275-83.

Pettersson B, Adami HO, Bergstrom R, Johansson ED. Menstruation span--a time-limited risk factor for endometrial carcinoma. Acta Obstet Gynecol Scand 1986; 65:247-55.

Prior P and Waterhouse JA. Multiple primary cancers of the breast and ovary. Br J Cancer 1981; 44:628-636.

Reimer RR, Hoover R, Fraumeni JF Jr, Young RC. Second primary neoplasms following ovarian cancer. J Natl Cancer Inst 1978; 61:1195-7.

Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Edwards BK. Eds. SEER Cancer Statistics Review, 1973-1998. National Cancer Institute, NIH, Bethesda, MD. 2001.

Riman T, Dickman PW, Nilsson S, Correia N, Nordlinder H, Magnusson CM, Weiderpass E, Persson IR. Hormone replacement therapy and the risk of invasive epithelial ovarian cancer in Swedish women. J Natl Cancer Inst 2002; 94:497-504.

Risinger JI, Barrett JC, Watson P, Lynch HT, Boyd J. Molecular genetic evidence of the occurrence of breast cancer as an integral tumor in patients with the hereditary nonpolyposis colorectal carcinoma syndrome. Cancer 1996; 77:1836-1843.

Roa BB, Boyd AA, Volcik K, Richards CS. Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. Nat Genet 1996; 14:185-7.

Rodriguez C, Tatham LM, Calle EE, Thun MJ, Jacobs EJ, Heath CW Jr. Infertility and risk of fatal ovarian cancer in a prospective cohort of US women. Cancer Causes Control. 1998; 9:645-51.

Rodriguez C, Patel AV, Calle EE, Jacob EJ, Thun MJ. Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. JAMA 2001; 285:1460-1465.

Rutanen EM. Insulin-like growth factors in endometrial function. Gynecol Endocrinol. 1998; 12:399-406.

Rutqvist, LE, Johansson, H, Signomklao, T, et al. Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. J Natl Cancer Inst 1995; 87:645-651.

Sandles LG, Shulman LP, Elias S, Photopulos GJ, Smiley LM, Posten WM, Simpson JL. Endometrial adenocarcinoma: genetic analysis suggesting heritable site-specific uterine cancer. Gynecol Oncol 1992; 47:167-71.

Sasco AJ. Epidemiology of breast cancer: an environmental disease? APMIS 2001; 109: 321-32.

Schlesselman JJ. Risk of endometrial cancer in relation to use of combined oral contraceptives. A practitioner's guide to meta-analysis. Hum Reprod 1997; 12:1851-63.

Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Estrogen-progestin replacement and risk of breast cancer. JAMA 2000; 284:691-4.

Schildkraut JM, Thompson WD. Relationship of epithelial ovarian cancer to other malignancies within families. Genet Epidemiol 1988; 5:355-67.

Schildkraut JM, Risch N, Thompson WD. Evaluating genetic association among ovarian, breast, and endometrial cancer: evidence for a breast/ovarian cancer relationship. Am J Hum Genet 1989; 45:521-9.

Schorge JO, Mahoney NM, Miller DS, Coleman RL, Muller CY, Euhus DM, Tomlinson GE. Germline BRCA1-2 mutations in non-Ashkenazi families with double primary breast and ovarian cancer. Gynecol Oncol 2001; 83:383-7.

Schottenfeld D and Berg J. Incidence of multiple primary cancers. IV. Cancers of the female breast and genital organs. J Natl Cancer Inst 1971; 46:161-170.

Scott RJ, McPhillips M, Meldrum CJ, Fitzgerald PE, Adams K, Spigelman AD, du SD, Tucker K, Kirk J. Hereditary nonpolyposis colorectal cancer in 95 families: differences and similarities between mutation-positive and mutation-negative kindreds. J Hum Genet 2001; 68:118-127.

Shattuck-Eidens D, McClure M, Simard J, Labrie F, Narod S, Couch F, Hoskins K, Weber B, Castilla L, Erdos M, et al. A collaborative survey of 80 mutations in the

BRCA1 breast and ovarian cancer susceptibility gene. Implications for presymptomatic testing and screening. JAMA 1995; 273:535-41.

Simard J, Tonin P, Durocher F, Morgan K, Rommens J, Gingras S, Samson C, Leblanc JF, Belanger C, Dion F, et al. Common origins of BRCA1 mutations in Canadian breast and ovarian cancer families. Nat Genet 1994; 8:392-8.

Steichen-Gersdorf E, Gallion HH, Ford D, Girodet C, Easton DF, DiCioccio RA, Evans G, Ponder MA, Pye C, Mazoyer S, et al. Familial site-specific ovarian cancer is linked to BRCA1 on 17q12-21. Am J Hum Genet 1994; 55:870-5.

Storm H.H., Ewertz M., Second cancer following cancer of the female genital system in Denmark, 1943-80. Natl Cancer Inst Monogr 1985; 68:331-40.

Stratton JF, Pharoah P, Smith SK, Easton D, Ponder BA. A systematic review and meta-analysis of family history and risk of ovarian cancer. Br J Obstet Gynaecol 1998; 105:493-9.

Strong LC. Genetic etiology of cancer. Cancer 1977; 40:438-444.

Struewing JP, Abeliovich D, Peretz T, Avishai N, Kaback MM, Collins FS, Brody LC. The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. Nat Genet 1995; 11:198-200.

Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, Timmerman MM, Brody LC, Tucker MA. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 1997; 336:1401-8.

Starink TM, van der Veen JP, Arwert F, de Waal LP, de Lange GG, Gille JJ, Eriksson AW. The Cowden syndrome: a clinical and genetic study in 21 patients. Clin Genet 1986; 29:222-33.

Szabo CI, King MC. Population genetics of BRCA1 and BRCA2. Am J Hum Genet 1997; 60:1013-20.

Tavtigian SV, Simard J, Rommens J, Couch F, Shattuck-Eidens D, Neuhausen S et al. The complete BRCA2 gene and mutations in chromosome 13q-linked kindreds. Nat Genet 1996; 12:333-7.

Tonin PN, Mes-Masson AM, Futreal PA, Morgan K, Mahon M, Foulkes WD, Cole DE, Provencher D, Ghadirian P, Narod SA. Founder BRCA1 and BRCA2 mutations in French Canadian breast and ovarian cancer families. Am J Hum Genet 1998; 63:1341-51.

Teppo L, Pukkala E, and Saxen E. Multiple cancer--an epidemiologic exercise in Finland. J Natl Cancer Inst 1985; 75:207-217.

Thompson WD, Schildkraut JM. Family history of gynaecological cancers: relationships to the incidence of breast cancer prior to age 55. Int J Epidemiol 1991; 20:595-602.

Thompson D, Easton D. Variation in cancer risks, by mutation position, in BRCA2 mutation carriers. Am J Hum Genet 2001; 68:410-9.

Thorlacius S, Sigurdsson S, Bjarnadottir H, Olafsdottir G, Jonasson JG, Tryggvadottir L, Tulinius H, Eyfjord JE. Study of a single BRCA2 mutation with high carrier frequency in a small population. Am J Hum Genet 1997; 60:1079-84.

Tokuoka S, Kawai K, Shimizu Y, Inai K, Ohe K, Fujikura T, Kato H. Malignant and benign ovarian neoplasms among atomic bomb survivors, Hiroshima and Nagasaki, 1950-80. J Natl Cancer Inst 1987; 79:47-57.

Tonin P, Serova O, Lenoir G, Lynch H, Durocher F, Simard J, Morgan K, Narod S. BRCA1 mutations in Ashkenazi Jewish women. Am J Hum Genet 1995; 57:189.

van Leeuwen, FE, Benraadt, J, Coebergh, WW, et al. Risk of endometrial cancer after tamoxifen treatment of breast cancer. Lancet 1994; 343:448-452.

Vasen HF, Watson P, Mecklin JP, Jass JR, Green JS, Nomizu T, Muller H, Lynch HT. The epidemiology of endometrial cancer in hereditary nonpolyposis colorectal cancer. Anticancer Res 1994; 14:1675-8.

Vasen HF, Wijnen JT, Menko FH, et al: Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. Gastroenterology 1996; 110:1020-7.

Venn A, Jones P, Quinn M, Healy D. Characteristics of ovarian and uterine cancers in a cohort of in vitro fertilization patients. Gynecol Oncol 2001; 82:64-68.

Watson P, Lynch HT. Extracolonic cancer in hereditary nonpolyposis colorectal cancer. Cancer 1993; 71:677-85.

Watson P, Vasen HF, Mecklin JP, Jarvinen H, Lynch HT. The risk of endometrial cancer in hereditary nonpolyposis colorectal cancer. Am J Med 1994; 96:516-20.

Weiderpass E, Baron JA, Adami HO, Magnusson C, Lindgren A, Bergstrom R, Correia N, Persson I. Low-potency oestrogen and risk of endometrial cancer: a case-control study. Lancet 1999a; 353:1824-8.

Weiderpass E, Adami HO, Baron JA, Magnusson C, Bergstrom R, Lindgren A, Correia N, Persson I. Risk of endometrial cancer following estrogen replacement with and without progestins. J Natl Cancer Inst 1999b; 91:1131-7.

Weiderpass E, Persson I, Adami HO, Magnusson C, Lindgren A, Baron JA. Body size in different periods of life, diabetes mellitus, hypertension, and risk of postmenopausal

endometrial cancer (Sweden). Cancer Causes Control 2000; 11:185-92.

Weiss NS, Cook LS, Farrow DC, et al. Ovarian cancer. In: Schottenfeld D, Fraumeni JF, editors. Cancer Epidemiology and Prevention. New York: Oxford University Press, 1996; pp. 1040-57

Whittemore AS, Harris R, and Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. Am J Epidemiol 1992; 136: 1184-1203.

Wignall BK and Fox AJ. Mortality of female gas mask assemblers. Br J Ind Med 1982; 39:34-38.

Wong C, Hempling RE, Piver MS, Natarajan N, Mettlin CJ. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. Obstet Gynecol 1999; 93:372-376.

Wooster R, Neuhausen SL, Mangion J, Quirk Y, Ford D, Collins N, Nguyen K, Seal S, Tran T, Averill D, et al. Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. Science 1994; 265:2088-90.

Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, Collins N, Gregory S, Gumbs C, Micklem G. Identification of the breast cancer susceptibility gene BRCA2. Nature 1995; 378:789-92.

Wright CDP, Compston JE. Tamoxifen: oestrogen or anti-oestrogen in bone? QJM 1995; 88:307-310.

Ziogas A, Gildea M, Cohen P, Bringman D, Taylor TH, Seminara D et al. Cancer risk estimates for family members of a population-based family registry for breast and ovarian cancer. Cancer Epidemiol Biomarkers Prev 2000; 9:103-11.

Family History of Breast Cancer as a Determinant of the Risk of Developing Endometrial Cancer: A Nationwide Cohort Study

Neely Kazerouni, M.P.H.[1,2,a]

Catherine Schairer, Ph.D.[1]

Heidi B. Friedman, Ph.D.[2]

James V. Lacey, Jr., Ph.D.[1]

Mark H. Greene, M.D.[1]

Author Affiliations: [1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rm 7022, Executive Plaza South, 6120 Executive Blvd, Rockville, MD 20852, USA; [2]Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814-4799, USA; [a]Current address: Centers for Disease Control and Prevention, 1600 Clifton Rd., MS E-17, Atlanta, GA. 30329.

Corresponding author: Mark H. Greene, M.D., Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rm 7022, Executive Plaza South, 6120 Executive Blvd, Rockville, MD 20852, USA.

Telephone: 301-594-7642, Fax: 301-496-1854, E-mail: greenem@mail.nih.gov

Keywords: endometrial cancer; family history; breast cancer; cohort study.

Running title: Family history of breast cancer and endometrial cancer risk.

ABSTRACT

Background--Although endometrial and breast cancers share some of the same reproductive, hormonal, and genetic risk factors, it is not well established if a family history of breast cancer is associated with endometrial cancer risk. We examined this association among 37,583 women, who were former participants in a national breast cancer screening program and were then selected for additional follow-up (average: 13.8 years) after the screening study had been completed. There were 648 women with endometrial cancer identified during the follow-up period (1979-1998).

Methods—This prospective cohort study collected information on the breast cancer history of mothers, sisters, daughters, aunts, and grandmothers of the participants. Data on the number of affected relatives, their age, and breast cancer laterality were also collected during the last three phases of the study. Poisson regression analyses were used to derive rate ratios and 95% confidence intervals.

Results--Controlling for attained age, menopausal status, race, body mass index, breast cancer diagnosis, and family size, the presence of breast cancer in a first-degree (RR= 0.96, 95% CI= 0.78-1.2) or a second-degree (RR=1.0, 95% CI=0.81-1.2) relative did not influence the risk of developing endometrial cancer. In addition, the risk of endometrial cancer did not vary by age of the relative at breast cancer diagnosis or by the number of affected relatives with breast cancer. However, there was a non-significant increase in the risk of endometrial cancer among women with a 1st degree relative with bilateral breast cancer (RR=1.4, 95% CI= 0.84-2.4) but not among women with a 1st degree relative with unilateral breast cancer (RR=0.83, 95% CI=0.62-1.1). Women with a personal history of

prior breast cancer were more likely to develop endometrial cancer during the course of follow-up (RR=1.3; 95% CI=1.1-1.7), but even in this subgroup, family history of breast cancer did not confer additional risk of endometrial cancer.

Conclusions--These results do not provide support for the hypothesis that a family history of breast cancer is an important determinant of the risk of developing endometrial cancer.

INTRODUCTION

Despite recent declines in its incidence, endometrial cancer remains the most common cancer of the female reproductive tract in the United States (1) and in the Western world (2). Well-established risk factors include exposure to unopposed estrogen, older age, nulliparity, obesity, and smoking (3). There are inconsistent reports on the association between endometrial cancer risk and family history of any cancer. Most of the familial studies of endometrial cancer among younger (20-54 year old) women have indicated an association with a family history of endometrial cancer (4-6); however, this association among older (55-69 year old) women has been inconsistent (7-10). Olson et al. (7) showed that neither family history of cancer (e.g., endometrium, colon, or breast) overall nor at any specific site was a risk factor in postmenopausal women, whereas Nelson et al. (9) reported a significantly higher risk of endometrial cancer among women with a family history of any of the selected sites (i.e., uterine, breast, colon, or ovarian cancer).

Endometrial cancer and breast cancer share some of the same reproductive and hormonal risk factors, such as nulliparity and exposure to unopposed estrogen (11-18). Reports on double primary cancers in the same individual provide further evidence for an etiologic

association between breast cancer and endometrial cancer (19-21).

In addition, it seems likely that there are shared genetic components involved in the etiology of at least some endometrial and breast cancer cases. Cowden syndrome and hereditary non-polyposis colorectal cancer (HNPCC) are genetic disorders which are said to include a predisposition to both endometrial and breast cancer in genetically at-risk family members (22-25).

However, the familial association between breast and endometrial cancer is uncertain. Lynch et al. (26) have identified families in which there are high frequencies of both breast and endometrial cancer. Anderson et al. (27) showed a significant excess risk of breast cancer among study participants with a family history of endometrial cancer. On the other hand, Parazzini et al. (28) found no association between family history of endometrial cancer in first-degree relatives and the risk of breast cancer. In addition, Kelsey et al. (10) found no indication of an increased frequency of breast cancer in the first-degree female relatives of women with endometrial cancer.

To investigate further the hypothesis of an association between **family history of breast cancer** and the **risk of developing endometrial cancer**, we analyzed data from a large prospective cohort of women with detailed information regarding the number and relationship of relatives affected with breast cancer, their age at breast cancer diagnosis, and breast cancer laterality.

MATERIALS AND METHODS

The NCI BCDDP Follow-up Study

The Breast Cancer Detection Demonstration Project (BCDDP), sponsored by the

American Cancer Society and the National Cancer Institute (NCI), was a breast cancer screening program conducted between 1973 and 1980. The BCDDP provided up to five annual breast examinations to 283,222 women at 29 screening centers in 27 cities throughout the United States (29). Over 99% of the participants were between the ages of 35 and 74 when they entered the screening program, with a median age of 50 years. The NCI began a Follow-up Study of a subset (n=64,182) of the BCDDP participants in 1979, which included: (1) all women who were diagnosed with breast cancer during the BCDDP (n=4,275); (2) all women who had a breast surgery performed during the screening program with no evidence of malignant breast disease (n=25,114); (3) all women who had received a recommendation by the project for a surgical consultation, but who did not have either a biopsy or aspiration performed (n=9,628); and (4) a sample of women who were not recommended for surgical consultation and did not undergo a biopsy (n=25,165).

The Follow-up Study was conducted in four phases. Phase I, carried out between 1979 and 1986, involved the administration of a baseline and up to six annual telephone interviews by the personnel at the BCDDP screening centers. Between 1987 and 1998, phase II (1987-1989), III (1993-1995), and IV (1995-1998) data collection was conducted through self-administered mailed questionnaires to all participants not known to be dead. In addition, attempts were made to conduct follow-up interviews by telephone for all non-respondents to the mailed questionnaires.

Data on race and education were available from screening visits between 1973-1979. Information collected from phase I of the study included age at menarche, number of live births, age at first live birth, ever use of oral contraceptives (if yes: years taken and age at first use), age at menopause, ever use of female hormones other than birth control pills (if yes: reasons for use, number of years taken, and age at first use), family history of breast

cancer in specific blood relatives (mother, sister, daughter, grandmother, aunt) including the number in each category affected with breast cancer, menopausal status (including date and reason for periods stopping; menopause was defined as no period having occurred within the three months prior to interview), removal of the uterus and/or ovaries (if yes: year of surgery), and breast biopsy resulting in either benign or malignant diagnoses. Information on all these factors, except for the first four variables was also collected in phases II-IV.

The following information, *not collected during phase I*, was collected during phases II, III, and IV: a more detailed family history of breast cancer, including an enumeration of all first and second-degree relatives (including half-sisters and both maternal and paternal lineage grandmothers and aunts), the relative's age at breast cancer diagnosis and information regarding whether the breast cancer was unilateral or bilateral; ever use of estrogen and progestin pills in the same month (if yes: age at first use, total duration of use, and number of days in the month progestin pills were taken); medical history, including diabetes, osteoporosis, bone fractures, new cancers (including date of diagnosis); date of first diagnosis of endometrial cancer; tobacco and alcohol use; physical parameters, including both "usual" and current adult height, weight and body shape. Finally, data regarding recent blood pressure and age at last childbirth were available from phase III.

During each phase, pathology reports were sought to objectively confirm self-reported cancers. In addition, the cohort was linked periodically to the National Death Index (NDI), and to selected population-based cancer registries, with the last known address of each participant used as her state of residence. Death certificates were retrieved and coded for cause of death during the first three phases of the study. During phase IV, cause of death was obtained from coding done by the NDI.

Analytic Cohort

Study population: Of the 64,182 women selected for participation in the Follow-up Study, 61,431 (95.7 percent) completed a baseline interview. Women with a diagnosis of endometrial cancer or who had hysterectomy *before* the baseline interview were excluded from the analytic cohort. This yielded 37,583 women who were eligible for inclusion in the current analysis. Of the 37,583 eligible women at baseline, 31,568 (84%), 27,526 (73%), and 26,225 (70%) completed the phase II, III, and IV interviews. Missing phase II questionnaires were due to death (4.9%), illness (0.8%), refusal (3.8%), and inability to contact before the end of the questionnaire period (6.5%). The corresponding proportions for missing phase III and IV questionnaires were 11.1%, 0.9%, 4.5%, and 10.5%; and 14.9%, 1.1%, 1.5%, and 12.6%. Seventy one percent (n=26,780) of those who answered the baseline interview (n=37,583) and 74 percent (n=23,324) of those who answered the phase II interview (n=31,569) in the endometrial cancer Follow-up Study were linked to state cancer registries. Most study participants were White (87 percent), with small percentages of Black (4 percent), Asian-American (5 percent), and Hispanic (2 percent) participants.

Analytic Data Set

***Case definition*:** Endometrial cancer cases (ICD_O codes 179.0, 179.9, 182.0, and ICD_9 codes 179X, 179.9, 182.0, 183.8, 183.9, 233.2) were identified through self-report on the follow-up questionnaires (phases II, III, and IV), pathology reports, death certificates, and state cancer registries.

Of the 648 women with endometrial cancer identified, 468 (72%) were identified by self-report on the follow-up questionnaires; 90% of these were confirmed by pathology reports (n=404), state cancer registries (n= 16), or death certificates (n=1). Independent confirmation was unavailable for 47 self-reports. Thirty-nine cases were ascertained by

pathology reports only, 46 cases were identified by death certificates obtained from the NDI (of these, state cancer registry information provided additional confirmation for 16 cases), and 95 cases were found only by matching study participants to various state cancer registries data files.

Statistical Analyses

The Follow-up Study began upon completion of the baseline interview. Person-years accrued until the earliest of the following dates: a) hysterectomy, b) endometrial cancer diagnosis, c) study end date, which was either the date of completion of the phase IV questionnaire or for non-respondents to phase IV, the estimated date that they would have completed the phase IV questionnaire (95-98) if still alive (i.e., depending on when they completed the phase III questionnaire, 93-95), and d) date of death or date of state cancer registry diagnosis of endometrial cancer if both of these dates were before the study end date. To assign dates of cancer diagnosis for cases identified by death certificates only, we used time since onset of disease from the death certificate, medical information from earlier interviews, date of hysterectomy, if the individual had this procedure done, or date of death if no other information was available.

All of the family history variables were analyzed as time-dependent variables in the analyses. Women who reported breast cancer in a sister, mother, and/or daughter were classified as having a "first-degree family history" and those who reported breast cancer in a grandmother, and/or aunt were classified as having "second-degree family history." Study participants were defined to have a family history at their age at the midpoint

between first report of exposure (i.e., family history of breast cancer) and the prior interview or questionnaire.

Rate ratios (RR) and 95 percent confidence intervals (CI) were estimated by Poisson regression. The reference category for all the analyses comprised women who did not have relatives with breast cancer in that category. Time-dependent variables: attained age, body mass index (BMI: weight divided by height squared, kg/m^2), menopausal status, breast cancer diagnosis, duration of oral contraceptive use, hormone replacement therapy use (ever), duration of estrogen only use, hypertension, diabetes, smoking status (never, current, former), and time-independent variables: education, race, parity, age at menarche, age at first live birth, age at last birth, and age at natural menopause were each considered as potential confounders for the family history variables. Although there was no evidence of confounding by variables other than attained age, final models included adjustment for a combination of time-dependent (attained age, menopausal status, a personal history of breast cancer, and BMI) and time-independent (race and family size) variables that were associated with either endometrial cancer or family history. Further adjustment for other risk factors did not alter the risk estimates.

RESULTS

The mean duration of follow-up was 13.8 years, with a median of 15.8 years, a maximum of 19.8 years, and a minimum of less than one year. During prospective follow-up of the cohort, 518,747 person-years of observation were accumulated for the 37,583 participants. The average age at the start of follow-up was 55 years.

Fifty-six percent of person-years were associated with no breast cancer family history of any type, 29% occurred in women with some family history of breast cancer (i.e., first-degree, second-degree or both), and 15% were associated with an uncertain or unascertained family history. Eighty-one percent of accumulated person-years were associated with no first-degree family history of breast cancer, 17% occurred in women with a first-degree family history, and 2% were associated with an uncertain or unascertained first-degree family history; the corresponding figures for a second-degree family history were 64%, 17%, and 19%.

Table 1 summarizes the distribution of person-time by first-degree family history of breast cancer, stratified by risk factors for endometrial cancer. Person-years associated with a first-degree family history did not vary meaningfully by most factors. A greater percentage of person-years associated with a first-degree family history was evident for older attained age and a personal history of breast cancer. Moreover, slightly greater percentages of person-years associated with race, higher BMI, and menopausal status were also associated with a first-degree family history.

Rate ratios of endometrial cancer associated with different categories of breast cancer family history are shown in Table 2. All the analyses for second-degree family history categories also included adjustments for a first-degree family history. In general, there were no associations between category of breast cancer family history and the risk of endometrial cancer:

- The number of family members with breast cancer did not alter the risk of

endometrial cancer;

- The same analyses excluding unconfirmed cases or cases diagnosed subsequent to the last questionnaire showed no associations;
- Similar associations between family history of breast cancer and the risk of endometrial cancer were found among women with and without a *personal* history of breast cancer; and
- The rate ratio for women with both a first- and a second-degree relative with breast cancer was neither elevated nor significant.

In all these analyses, the women who did not have relatives with breast cancer in the category under analysis formed the reference group for each group, as has been done in previously-published studies of this kind; however, choosing women with no first- and second-degree family history as the comparison groups made no difference in results (data not shown).

Because both the diagnosis of breast cancer at an earlier than usual age and the development of cancer in both breasts (i.e., bilateral breast cancer) are considered harbingers of a genetic predisposition to breast cancer, we analyzed the risk of endometrial cancer taking this information into account. As shown in Table 3, women reporting a bilateral breast cancer in any first degree relative (RR=1.4, 95% CI: 0.8-2.4), or mothers (RR=1.5, 95% CI: 0.7-3.1), or sisters (RR=1.4, 95% CI: 0.7-2.7) all had non-significantly elevated rates compared to women without a family history of breast cancer in that category. With regard to age at breast cancer diagnosis among family members, there were no associations with endometrial cancer when women with early- and later-

onset breast cancer were compared to women without a family history of breast cancer. As has been previously reported, women in this cohort with a prior personal history of breast cancer were at significantly increased risk of developing endometrial cancer during prospective follow-up (RR=1.3; 95% CI=1.1-1.7). This was a subgroup in which we had a prior hypothesis that the influence of family history of breast cancer on the risk of endometrial cancer might be more readily detected, but that proved not to be the case, either overall (data not shown), or when considering early age at breast cancer diagnosis among first-degree family members. However, in this group of women, individuals reporting a bilateral breast cancer in any first-degree relative (n=4) had a non-significantly elevated rate (RR=1.8, 95% CI: 0.6-5.2) of endometrial cancer as compared with women without a first-degree family history of breast cancer.

DISCUSSION

In this nationwide prospective study of 37,583 women, reported family history of breast cancer did not confer an increased risk of endometrial cancer. This null result was found despite our having detailed information on breast cancer family history, including age at diagnosis and bilaterality in the affected relatives. Furthermore, the cohort was large, as was the number of women who developed endometrial cancer during follow-up, which averaged 13.8 years per participant.

Our results are consistent with the reports of two other large cohort studies (7,9) but inconsistent with a family study (26). The study by Lynch et al. (26), included highly

selected families with two or more members affected with breast cancer and who therefore had a relatively strong predispositions for cancer. On the other hand, two reports have been published from the Iowa Women's Health Study (IWHS), a cohort whose participants are similar to those in the BCDDP, but who were recruited via different methods (i.e., use of Iowa Department of Transportation driver's license list). The IWHS collected family history information only at baseline, and there was no information about family size or age at onset of cancer in family members. However, the nested case-control analysis (7) showed a slight, non-significant increase in endometrial cancer risk among women with a first-degree family history of breast cancer (OR=1.2, 95% CI: 0.6-2.5).

A major strength of our study was the evaluation of endometrial cancer risk in relation to a family history of *bilateral breast cancer, the number of affected relatives and their age at breast cancer diagnosis*. These features of breast cancer are of great potential interest in assessing whether a family history might increase endometrial cancer risk through a genetic mechanism (30-36). In that regard, it was of interest to note that endometrial cancer risk among women reporting bilateral breast cancer in a first degree relative (mother/sister and/or daughter) was elevated by 40%, an increase that was not statistically significant. However, there were no associations between endometrial cancer risk and age at breast cancer diagnosis among family members and the number of affected relatives. Our data do not permit us to distinguish between this "increase" being false, a consequence of intensive data analysis with multiple comparisons having been made, and its being a true finding compromised by low statistical power in this subgroup.

The occurrence of multiple persons with cancer in the members of a family could reflect a shared genetic predisposition, a common environmental exposure, a more complex interaction between genes and environment, or chance. Because we did not collect information on environmental risk factors from relatives of the participants and because we had a relatively small number of participants in subgroups of particular interest, we could not distinguish among these possibilities in evaluating the modest association between endometrial cancer risk and history of bilateral breast cancer in a first degree relative. It is notable, however, that this elevated risk was consistently observed across categories of women with any first-degree relative, mother, or sister with a bilateral breast cancer.

There are two genetic syndromes, Cowden's disease and HNPCC, which some (but not all) investigators have suggested may include a predisposition to both endometrial and breast cancers among members of the same family (24-27,39-41). However, despite the suggestion that breast cancer may be part of the HNPCC syndrome in at least a subset of families (24,25,37-39), other reports do not support the hypothesis that HNPCC family members are at an increased risk of breast cancer (9,40,41). The most recent study of this question provided evidence that at least some of the breast cancer that arises in women with HNPCC appears to be sporadic in nature, rather than caused by mutations in one of the mismatch repair genes (42). Because we collected information related to family history of cancers other than breast cancer only during phase IV of this study, we were unable to assess whether any of the endometrial cancer cases in our study occurred in families likely to be affected by Cowden syndrome, HNPCC, or by other familial cancer

syndromes.

Another possible explanation for our null results was the absence of younger women from the cohort. Only 9% of the accumulated woman-years of observation in this cohort were accrued by women less than age 50. As noted previously, a younger-than-usual age at cancer diagnosis is one of the cardinal features of most hereditary cancer syndromes. The small contribution of such women to the events observed in this study may have compromised our ability to detect a breast cancer pattern suggestive of a genetic disorder. However, Schildkraut et al (6) found no elevated relative risk for breast cancer among mothers and sisters of endometrial cancer cases younger than 55 years of age (RR=1.2, 95% CI: 0.7-2.2).

The endometrial cancer risk factors identified in this study are consistent with those identified in previous studies (10,13,14,17,43-46). The finding that women with a personal history of breast cancer had a significant, 30% excess risk for endometrial cancer is interesting and consistent with earlier studies (21,47,48). This could suggest that shared environmental, hormonal and/or genetic risk factors may be involved in the pathogenesis of these cancers. Because we adjusted for attained age, duration of menopausal estrogen use, menopausal status, BMI, and parity in assessing risk of endometrial cancer associated with a personal history of breast cancer, it is unlikely that these shared risk factors account for the association.

It is also possible that the increased risk of double primaries of the breast and

endometrium could be due to medications that increase the risk of endometrial cancer, such as hormone replacement therapy with unopposed estrogen (49) and adjuvant therapy with tamoxifen (50-53). An increased incidence of endometrial cancer in women with breast cancer has been reported (54,55). Since the early 1970s, tamoxifen has been widely used for the treatment of advanced breast cancer and in the 1980s, adjuvant tamoxifen therapy became the standard of care for women with stage II breast cancer. Cancer treatment trials using tamoxifen have shown an excess risk of up to 2-fold for endometrial cancer among breast cancer patients treated with adjuvant tamoxifen (52,53,56,57). Because we did not collect information on tamoxifen use or other hormonal therapies for breast cancer treatment, we were unable to evaluate whether the excess risk of endometrial cancer among participants with breast cancer is due to tamoxifen use or shared genetic or environmental factors that we did not adjust for. However, the bulk of the person-years of observation in the current study were accrued in an era when the adjuvant use of tamoxifen in the treatment of the earliest stages of breast cancer was not yet widespread.

Several methodologic issues need to be considered in interpreting our results. Although most data were obtained prospectively, some of the information on family history of breast cancer was reported by cases on questionnaires that were completed after their diagnosis of endometrial cancer. Thus, it is possible that cases differentially recalled their family history of breast cancer compared with non-cases. However, a methodological study found no difference in the reporting of breast cancer in family members between patients with and without breast cancer (58). It is likely that these results would also

pertain to reporting of family history of breast cancer by patients with and without endometrial cancer. In addition, we did not have complete information on a family history of breast cancer and other risk factors for some participants who did not complete all questionnaires. However, there was no difference in loss to follow-up according to the family history of breast cancer data. Finally, no attempt was made to obtain objective verification of the breast cancers that were reported by study participants to have occurred among their relatives. However, prior studies have shown that the accuracy of reported occurrences of breast cancer in family studies is very high, in the range of 83%-95% (58-62); reporting of family history of breast cancer in a second-degree relative is less accurate (62,63). We are therefore reasonably confident regarding the reliability of the reported family history information, particularly among first-degree relatives.

In summary, our cohort study revealed no overall association between a family history of breast cancer and endometrial cancer risk. Although we found a non-significant increased risk for women with a first-degree (mother and/or sisters) family member with bilateral breast cancer, we did not see any associations with other features of various hereditary cancer syndromes, such as early age of onset and high incidence of multiple persons with breast cancer among family members. Thus, a family history of breast cancer does not seem to be an important endometrial cancer risk factor, although a *personal* history of breast cancer does increase the risk of developing endometrial cancer by approximately 30%.

Acknowledgements

We thank the BCDDP participants; Susan Englehart, Catherine Ann Grundmayer, and the members of the BCDDP Staff at Westat Inc, Rockville, MD; and Leslie Carroll, Franklin Demuth, Jennifer Boyd-Morin, and David Campbell, Jr. of IMS Inc, Silver Spring, MD, for computer support. We acknowledge the California Department of Health Services, Cancer Surveillance Section; Florida Cancer Data System, under contract to the Florida Department of Health; Maryland Cancer Registry, Maryland Department of Health and Mental Hygiene; Michigan Cancer Surveillance Program within the Division of Vital Records and Health Statistics, Michigan Department of Community Health; Pennsylvania Department of Health; Tennessee Cancer Registry; Texas Department of Health; and the states of Arizona, Georgia, Hawaii, Idaho, Iowa, New Jersey, New York, North Carolina, Ohio, Oregon, and Rhode Island for providing data from their cancer registries for use in these analyses. The opinions or assertions contained in this manuscript are the personal conclusions of the authors and are not to be construed as official or reflecting the views of any state agency listed above, the United States Department of Defense, or the Uniformed Services University of the Health Sciences.

REFERENCES

1. Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Edwards BK (eds). SEER Cancer Statistics Review, 1973-1999, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1973_1999/, 2002.

2. Parkin DM. Epidemiology of cancer: global patterns and trends. Toxicol Lett 1998; **102-103**:227-34.

3. Parazzini F, La Vecchia C, Bocciolone L, Franceschi S. The epidemiology of endometrial cancer. Gynecol Oncol 1991;41(1):1-16.

4. Parslov M, Lidegaard O, Klintorp S, Pedersen B, Jonsson L, Eriksen PS, Ottesen B. Risk factors among young women with endometrial cancer: a Danish case-control study. Am J Obstet Gynecol 2000;**182**:23-9.

5. Gruber SB, Thompson WD. A population-based study of endometrial cancer and familial risk in younger women. Cancer and Steroid Hormone Study Group. Cancer Epidemiol Biomarkers Prev 1996;**5**:411-417.

6. Schildkraut JM, Risch N, Thompson WD. Evaluating genetic association among ovarian, breast, and endometrial cancer: evidence for a breast/ovarian cancer relationship. Am J Hum Genet 1989;**45**:521-9.

7. Olson JE, Sellers TA, Anderson KE, Folsom AR. Does a family history of cancer increase the risk for postmenopausal endometrial carcinoma? A prospective cohort study and a nested case-control family study of older women. Cancer 1999;**85**:2444-2449.

8. Parazzini F, La Vecchia C, Moroni S, Chatenoud L, Ricci E. Family history and the risk of endometrial cancer. Int J Cancer 1994;**59**(4):460-2.

9. Nelson CL, Sellers TA, Rich SS, Potter JD, McGovern PG, Kushi LH. Familial clustering of colon, breast, uterine, and ovarian cancers as assessed by family history. Genet Epidemiol 1993;**10**:235-244.

10. Kelsey JL, LiVolsi VA, Holford TR, Fischer DB, Mostow ED, Schwartz PE, O'Connor T, White C. A case-control study of cancer of the endometrium. Am J Epidemiol 1982; **116**:333-342.

11. Sasco AJ. Epidemiology of breast cancer: an environmental disease? APMIS

2001;109 (5):321-32.

12. MacMahon B, Cole P, Lin TM, Lowe CR, Mirra AP, Ravnihar B, Salber EJ, Valaoras VG, Yuasa S. Age at first birth and breast cancer risk. Bull World Health Organ 1970;**43**:209-21.

13. MacMahon B. Risk factors for endometrial cancer. Gynecol Oncol 1974;2:122-9.

14. Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD, Lannom L, Hoover RN. Reproductive, menstrual, and medical risk factors for endometrial cancer: results from a case-control study. Am J Obstet Gynecol 1992;**167**:1317-25.

15. Lyon FA. The development of adenocarcinoma of the endometrium in young women receiving long-term sequential oral contraception. Am J Obstet Gynecol 1975;**123**:299-301.

16. Henderson BE, Casagrande JT, Pike MC, Mack T, Rosario I, Duke A. The epidemiology of endometrial cancer in young women. Br J Cancer 1983;**47**:749-56.

17. Hoover R, Fraumeni JF, Everson R, Myers MH. Cancer of the uterine corpus after hormonal treatment for breast cancer. Lancet 1976; **1**:885-7.

18. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. Obstet Gynecol 1995;**85**:304-13.

19. Curtis RE, Hoover RN, Kleinerman RA, Harvey EB. Second cancer following cancer of the female genital system in Connecticut, 1935-82. Natl Cancer Inst Monogr 1985;**68**:113-37.

20. Storm HH, Ewertz M. Second cancer following cancer of the female genital system in Denmark, 1943-80. Natl Cancer Inst Monogr 1985;**68**:331-40.

21. Harvey EB, Brinton LA. Second cancer following cancer of the breast in Connecticut, 1935-82. Natl Cancer Inst Monogr 1985;**68**:99-112.

22. Mutter GL, Lin MC, Fitzgerald JT, Kum JB, Baak JP, Lees JA, Weng LP, Eng C. Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. J Natl Cancer Inst 2000;**92**:924-930.

23. Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. J Med Genet 2000;**37**:828-30.

24. Risinger JI, Barrett JC, Watson P, Lynch HT, Boyd J. Molecular genetic evidence of the occurrence of breast cancer as an integral tumor in patients with the hereditary nonpolyposis colorectal carcinoma syndrome. Cancer 1996;**77**:1836-1843.

25. Scott RJ, McPhillips M, Meldrum CJ, Fitzgerald PE, Adams K, Spigelman AD, du SD, Tucker K, Kirk J. Hereditary nonpolyposis colorectal cancer in 95 families: differences and similarities between mutation-positive and mutation-negative kindreds. J Hum Genet 2001;**68**:118-127.

26. Lynch HT, Krush AJ, Lemon HM, Kaplan AR, Condit PT, Bottomley RH. Tumor variation in families with breast cancer. JAMA 1972;**222**:1631-1635.

27. Anderson DE, Badzioch MD. Familial breast cancer risks. Effects of prostate and other cancers. Cancer 1993;**72**:114-119.

28. Parazzini F, La Vecchia C, Negro E, Franceschi S, Tizzy L. Family history of breast, ovarian and endometrial cancer and risk of breast cancer. Int J Epidemiol 1993;**22**:614-618.

29. Baker LH. Cancer Detection Demonstration Project: Five-year summary report. CA Cancer J Clin 1982; **32**:194-225.

30. Anderson DE. A genetic study of human breast cancer. J Natl Cancer Inst 1972;**48**:1029-1034.

31. Anderson DE. Breast cancer in families. Cancer 1977;**40**:1855-60.

32. Anderson DE. Familial versus sporadic breast cancer. Cancer 1992;**70**:1740-6.

33. Ottman R, Pike MC, King MC, Casagrande JT, Henderson BE. Familial breast cancer in a population-based series. Am J Epidemiol 1986;**123**:15-21.

34. Claus EB, Risch NJ, Thompson WD. Age at onset as an indicator of familial risk of breast cancer. Am J Epidemiol 1990;**131**:961-72.

35. Tulinius H, Sigvaldason H, Olafsdottir G, Tryggvadottir L. Epidemiology of breast cancer in families in Iceland. J Med Genet 1992;**29**:158-164.

36. Lynch HT, Casey MJ, Shaw TG, Lynch JF. Hereditary Factors in Gynecologic Cancer. Oncologist 1998;**3**:319-338.

37. Lynch HT, Kimberling W, Albano WA, Lynch JF, Biscone K, Schuelke GS, Sandberg AA, Lipkin M, Deschner EE, Mikol YB. Hereditary nonpolyposis colorectal cancer (Lynch syndromes I and II). I. Clinical description of resource. Cancer 1985;**56**:934-938.

38. Lynch HT, Lanspa S, Smyrk T, Boman B, Watson P, Lynch J. Hereditary nonpolyposis colorectal cancer (Lynch syndromes I & II). Genetics, pathology, natural history, and cancer control, Part I. Cancer Genet Cytogenet 1991;**53**:143-160.

39. Itoh H, Houlston RS, Harocopos C, Slack J. Risk of cancer death in first-degree relatives of patients with hereditary non-polyposis cancer syndrome (Lynch type II): a study of 130 kindreds in the United Kingdom. Br J Surg 1990;**77**:1367-1370.

40. Watson P, Lynch HT. Extracolonic cancer in hereditary nonpolyposis colorectal cancer. Cancer 1993;**71**(3):677-85.

41. Vasen HF, Morreau H, Nortier JW. Is breast cancer part of the tumor spectrum of hereditary nonpolyposis colorectal cancer? Am J Hum Genet 2001;**68**(6):1533-5.

42. Müller A, Edmonston TB, Corao DA, Rose DG, Palazzo JP, Becker H, Fry RD, Rueschoff J, Fishel R. Exclusion of breast cancer as an integral tumor of hereditary nonpolyposis colorectal cancer. Cancer Res 2002;**62**:1014-1019.

43. Weiderpass E, Persson I, Adami HO, Magnusson C, Lindgren A, Baron JA. Body size in different periods of life, diabetes mellitus, hypertension, and risk of postmenopausal endometrial cancer (Sweden). Cancer Causes Control 2000;**11**:185-92.

44. Kvale G, Heuch I, Nilssen S. Reproductive factors and cancers of the breast and genital organs--are the different cancer sites similarly affected? Cancer Detect Prev 1991;**15**:369-77.

45. La Vecchia C, Franceschi S, Decarli A, Gallus G, Tognoni G. Risk factors for endometrial cancer at different ages. J Natl Cancer Inst 1984;**73**:667-71.

46. Austin H, Drews C, Partridge EE. A case-control study of endometrial cancer in relation to cigarette smoking, serum estrogen levels, and alcohol use. Am J Obstet Gynecol 1993; **169**(5):1086-91.

47. MacMahon B, Austin JH. Association of carcinomas of the breast and corpus uteri. Cancer 1969;**23**:275-80.

48. Adami HO, Krusemo UB, Bergkvist L, Persson I, Pettersson B. On the age-dependent association between cancer of the breast and of the endometrium. A nationwide cohort study. Br J Cancer 1987;**55**:77-80.

49. Hoover R, Fraumeni JF, Everson R, Myers MH. Cancer of the uterine corpus after hormonal treatment for breast cancer. Lancet 1976;**1**(7965):885-7.

50. Jordan VC, Assikis VJ. Endometrial carcinoma and tamoxifen: clearing up a controversy. Clin Cancer Res 1995;**1**:467-72.

51. Assikis VJ, Jordan VC. Gynecologic effects of tamoxifen and the association with endometrial carcinoma. Int J Gynaecol Obstet 1995;**49**:241-57.

52. Rutqvist LE, Johansson H, Signomklao T, Johansson U, Fornander T, Wilking N. Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. Stockholm Breast Cancer Study Group. J Natl Cancer Inst 1995;**87**:645-51.

53. Fornander T, Rutqvist LE, Cedermark B, Glas U, Mattsson A, Silfversward C, Skoog L, Somell A, Theve T, Wilking N, Wilking N, Askergren J, Hjalmar M-L. Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. Lancet 1989;**1**:117-20.

54. Schoenberg BS, Greenberg RA, Eisenberg H. Occurrence of certain multiple primary cancers in females. J Natl Cancer Inst 1969;**43**(1):15-32.

55. MacMahon B. Risk factors for endometrial cancer. Gynecol Oncol 1974;**2**(2-3):122-9.

56. Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. J Natl Cancer Inst 1994 **86**:527-37.

57. van Leeuwen FE, Benraadt J, Coebergh JW, Kiemeney LA, Gimbrere CH, Otter R, Schouten LJ, Damhuis RA, Bontenbal M, Diepenhorst FW, van den Belt-Dusebout AW,

van Tinteren H. Risk of endometrial cancer after tamoxifen treatment of breast cancer. Lancet 1994;**343**:448-52.

58. Parent ME, Ghadirian P, Lacroix A, Perret C. The reliability of recollections of family history: implications for the medical provider. J Cancer Educ 1997;**12**:114-120.

59. Eerola H, Blomqvist C, Pukkala E, Pyrhonen S, Nevanlinna H. Familial breast cancer in southern Finland: how prevalent are breast cancer families and can we trust the family history reported by patients? Eur J Cancer 2000;**36**:1143-8.

60. Douglas FS, O'Dair LC, Robinson M, Evans DG, Lynch SA. The accuracy of diagnoses as reported in families with cancer: a retrospective study. J Med Genet 1999;**36**:309-12.

61. Kerber RA, Slattery ML. Comparison of self-reported and database-linked family history of cancer data in a case-control study. Am J Epidemiol 1997;**146**:244-248.

62. Love RR, Evans AM, Josten DM. The accuracy of patient reports of a family history of cancer. J Chronic Dis 1985;**38**:289-93.

63. Theis B, Boyd N, Lockwood G, Tritchler D. Accuracy of family cancer history in breast cancer patients. Eur J Cancer Prev 1994;**3**:321-7.

Table 1. Distribution of person-years by first-degree family history of breast cancer according to selected factors in BCDDP endometrial cancer Follow-up Study, 1979-1998

Risk factor	Never 1st degree family history of breast cancer (%)	Ever 1st degree family history of breast cancer (%)	Unsure 1st degree family history of breast cancer (%)	Total person-years
Attained age (yrs)				
<50	85.0	14.0	1.0	47,881
50-54	83.1	15.4	1.6	72,040
55-59	81.6	16.5	1.9	100,680
60-64	80.3	17.7	2.0	101,318
65-69	78.9	19.0	2.1	82,058
70-74	77.7	20.1	2.2	55,842
75+	75.7	21.8	2.5	58,927
Race				
White	79.7	18.3	1.9	451,128
Hispanic	85.2	12.5	2.3	11,692
Black	83.7	14.5	1.7	19,998
Other	84.6	13.8	1.6	35,930
Body mass index (kg/m^2)				
<22.05	81.1	17.3	1.6	185,058
22.05-25.07	80.3	17.6	2.1	154,982
25.08-27.85	79.8	18.2	2.0	80,203
27.86-32.06	79.6	18.1	2.3	53,369
32.07+	78.8	19.0	2.2	26,508
Unknown	79.6	18.6	1.8	18,625
Personal history of breast cancer				
Never	81.3	16.8	1.9	468,590
Ever	71.4	26.3	2.3	50,157
Menopausal status				
Pre-menopause	83.5	15.1	1.4	65,740
Menopause	79.9	18.1	2.0	437,138
Unknown	79.9	17.3	2.8	15,869
1st-degree family size				
<4	82.6	15.4	2.0	237,784
4-5	78.1	20.3	1.6	134,371
6-7	74.9	23.5	1.6	50,616
8+	71.3	26.7	2.0	20,526
Unknown	83.5	14.2	2.3	75,451

Table 2. Rate ratios (RR) of endometrial cancer associated with family history of breast cancer in BCDDP endometrial cancer Follow-up Study, 1979-1998

Relative	No. of Person-Years	No. of Cases	Adjusted * RR (95% CI)
Any family history			
No history	283,382	352	1.0 (reference)
1 affected	111,368	138	0.9 (0.7-1.1)
2 or more affected	45,652	59	0.9 (0.7-1.2)
Any affected	157,020	197	0.9 (0.8-1.1)
Unknown	78,345	99	0.8 (0.6-1.0)
Any 1st degree			
No history	416,839	521	1.0 (reference)
1 affected	78,650	104	1.0 (0.8-1.2)
2 or more affected	13,331	15	0.8 (0.5-1.3)
Any affected	91,981	119	1.0 (0.8-1.2)
Unknown	9,927	8	0.6 (0.3-1.1)
Mother			
No history	458,967	577	1.0 (reference)
Mother affected	50,579	64	1.0 (0.8-1.3)
Unknown	9,201	7	0.5 (0.3-1.2)
Sister			
No history	467,353	583	1.0 (reference)
1 affected	38,600	50	0.9 (0.7-1.2)
2 or more affected	6,412	9	0.9 (0.5-1.8)
Any affected	45,012	59	0.9 (0.7-1.2)
Unknown	6,381	6	0.7 (0.3-1.6)
Daughter			
No history	509,734	638	1.0 (reference)
1 affected	3,307	4	0.7 (0.3-2.0)
2 or more affected	452	1	0.8 (0.1-7.8)
Any affected	3,759	5	0.8 (0.3-1.9)
Unknown	5,255	5	0.7 (0.3-1.6)
Any 2nd degree			
No history	333,569	404	1.0 (reference)
1 affected	68,458	84	1.0 (0.7-1.2)
2 or more affected	20,309	30	1.1 (0.8-1.7)
Any affected	88,767	114	1.0 (0.8-1.2)
Unknown	96,411	130	0.9 (0.8-1.2)
Grand mother			
No history	410,817	508	1.0 (reference)
1 affected	21,126	21	0.8 (0.5-1.3)
2 affected	1,196	2	1.2 (0.3-4.9)
Any affected	22,322	23	0.9 (0.6-1.3)
Unknown	85,609	117	1.0 (0.8-1.2)

Table 2. Rate ratios (RR) of endometrial cancer associated with family history of breast cancer in BCDDP endometrial cancer Follow-up Study, 1979-1998

Relative	No. of Person-Years	No. of Cases	Adjusted * RR (95% CI)
Aunt			
No aunt's history	376,329	449	1.0 (reference)
1 affected	59,104	72	1.0 (0.7-1.3)
2 or more affected	13,754	25	1.5 (1.0-2.3)
Any affected	72,858	97	1.1 (0.8-1.3)
Unknown	69,560	102	1.1 (0.9-1.4)

*Adjusted for number of relatives, attained age, BMI, personal breast cancer diagnosis, race, and menopausal status. The second-degree variables were also adjusted for a first-degree family history.
Women who did not have relatives with breast cancer in that category formed the reference group for each group.

Table 3. Rate ratios for endometrial cancer, 95% Confidence Intervals, number of cases and total person-years by age of diagnosis and disease laterality of relative with breast cancer

	First-Degree Relative					
	Age at Diagnosis*			Laterality Status		
Reference Group	<50	≥50	Unknown	Unilateral	Bilateral	Unknown
1.0	0.8	1.0	0.9	0.8	1.4	1.0
	(0.5-1.2)	(0.8-1.3)	(0.6-1.3)	(0.6-1.1)	(0.8-2.4)	(0.8-1.3)
CA/PY	24/23,292	69/46,193	25/22,280	49/42,948	15/8,349	55/41,562
Women with a personal history of breast cancer[φ]						
1.0	0.5	0.8	1.2	0.6	1.8	0.8
	(0.2-1.7)	(0.4-1.5)	(0.5-2.8)	(0.2-1.3)	(0.6-5.2)	(0.4-1.7)
CA/PY	3/3,187	10/6,862	6/3,053	6/5,924	4/1,351	9/5,932
	Mother with Breast Cancer					
	Mother's Age at Diagnosis*			Mother's Laterality Status		
Reference Group	<50	≥50	Unknown	Unilateral	Bilateral	Unknown
1.0	0.9	1.0	0.8	0.9	1.5	1.0
	(0.4-1.7)	(0.8-1.4)	(0.5-1.4)	(0.6-1.3)	(0.7-3.1)	(0.7-1.5)
CA/PY	8/7,622	42/29,301	14/13,814	28/24,290	7/4,274	29/22,509
	Sister with Breast Cancer					
	Sister's Age at Diagnosis*			Sister's Laterality Status		
Reference Group	<50	≥50	Unknown	Unilateral	Bilateral	Unknown
1.0	0.8	1.0	1.1	0.8	1.4	0.9
	(0.5-1.4)	(0.7-1.4)	(0.6-1.8)	(0.5-1.2)	(0.7-2.7)	(0.6-1.4)
CA/PY	14/13,707	30/20,349	15/11,015	24/20,630	9/4,558	26/20,224
	Daughter with Breast Cancer					
	Daughter's Age at Diagnosis*			Daughter's Laterality Status		
Reference Group	<50	≥50	Unknown	Unilateral	Bilateral	Unknown
1.0	0.7	---	1.3	0.5	1.1	1.2
	(0.2-2.2)	---	(0.3-5.4)	(0.1-2.1)	(0.1-9.0)	(0.3-5.1)
CA/PY	3/2,474	0	2/890	2/2,294	1/313	2/1,134

*Age at diagnosis is the age of youngest relative in that category with breast cancer.
All analyses are adjusted for attained age, race, menopausal status, BMI, number of relatives in each category (except mother's category), and personal breast cancer diagnosis (except the category of women with a personal history of breast cancer). [φ] The last variable was not included in the model.
Women who did not have relatives with breast cancer in that category formed the reference group for each group.

Family History of Breast Cancer as a Determinant of the Risk of Developing Ovarian Cancer: A Nationwide Cohort Study

Neely Kazerouni, M.P.H.[1,3]

Mark H. Greene, M.D. [2]

Heidi B. Friedman, Ph.D.[3]

James V. Lacey, Jr., Ph.D. [2]

Pamela J. Mink, Ph.D. [2]

Catherine Schairer, Ph.D. [2]

Author Affiliations: [1]Centers for Disease Control and Prevention, 1600 Clifton Rd., MS E-17, Atlanta, GA. 30329. [2]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rm 7022, Executive Plaza South, 6120 Executive Blvd, Rockville, MD 20852, USA; [3]Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814-4799, USA;

Corresponding author: Catherine Schairer, Ph.D. Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rm 8033, Executive Plaza South, 6120 Executive Blvd, Rockville, MD 20852, USA.

Telephone: 301-435-3979, Fax: 301-496-1854, E-mail: cs79u@nih.gov

Keywords: ovarian cancer; family history; BRCA1; BRCA2; breast cancer; cohort study.

Running title: Family history of breast cancer and ovarian cancer risk.

ABSTRACT

Purpose: Because breast and ovarian cancer are very closely associated in the BRCA1/2 cancer susceptibility syndromes, we assessed the role of a family history of breast cancer as a risk factor for the development of ovarian cancer in a general population setting.

Patients and Method: The women in the study (n=49,975) were former participants in a national breast cancer screening program who were selected for additional follow-up (1979-1998). During follow-up, 362 women with ovarian cancer were identified. We examined information on the breast cancer history of mothers, sisters, daughters, aunts, and grandmothers of the study participants as well as the number of relatives affected with breast cancer, their age at diagnosis, and breast cancer laterality. We used Poisson regression to estimate rate ratios and 95% confidence intervals to characterize the precision of these point estimates.

Results: Breast cancer in a first- or second-degree (RR=1.4, 95% CI=1.1-1.7), and any second-degree (RR=1.3, 95% CI=1.0-1.7) relative, increased the risk of ovarian cancer. Participants with two or more first-degree relatives with breast cancer also had a significantly increased risk (RR=1.8, CI=1.1-2.8). Risk was particularly high among women with 2 or more first-degree affected relatives, at least one of whom had bilateral breast cancer (RR=4.2, CI=1.7-10) or younger age (<50) at breast cancer diagnosis (RR=2.6, 95% CI=1.4-4.8), and among women with a personal history of breast cancer who also had a first-degree relative with younger age at breast cancer diagnosis (RR=3.5, 95% CI: 1.7-7.4).

Conclusion: These results provide support for the hypothesis that a family history of breast cancer is an important determinant of the risk of developing ovarian cancer.

INTRODUCTION

Ovarian cancer accounts for 4% of all cancers among women and is the second most common gynecologic cancer in the United States.[1] The established risk factors for ovarian cancer include older age, Jewish ancestry (i.e., BRCA1 and BRCA2 gene mutations), mismatch repair gene mutations in families with hereditary nonpolyposis colorectal cancer, family history of ovarian cancer, and hormonal and reproductive factors such as nulliparity, while multiparity and oral contraceptive use are associated with lower risk.[2-4]

It has been suggested that ovarian and breast cancers share a common genetic etiology.[5] The hereditary breast and ovarian cancer syndrome (HBOC) is an important genetic disorder that predisposes to both malignancies. Inherited mutations in the genes BRCA1 and BRCA2 are estimated to be responsible for most (80-90%) hereditary ovarian cancers[6-7] as well as the majority of hereditary breast cancers.[4,8-9]

There is a substantial body of evidence documenting an association between breast cancer and ovarian cancer in the same family. These studies demonstrate an excess risk of one cancer when there was a report of the other cancer in a family member.[10-18]

Several population-based epidemiologic studies (cohort, case control, and family studies) have addressed the association between ovarian cancer risk and family history of breast cancer (including the relative's age of breast cancer onset, and the number of affected relatives), but the results have been inconsistent.[10,12,14,16,19] In addition, no studies have looked at the risk of ovarian cancer as it may relate to the laterality of breast cancer in family members. These variables are of interest because they are felt to represent clinical clues to the presence of a hereditary cancer predisposition.

To investigate further the hypothesis that family history of breast cancer may increase the risk of developing ovarian cancer in the general population setting, we analyzed data from a large prospective cohort of women, from whom we obtained detailed information regarding the number and relationship of relatives affected with breast cancer, their age at breast cancer diagnosis, and breast cancer laterality.

PATIENTS AND METHODS

The NCI BCDDP Follow-up Study

The women in the study were former participants in the Breast Cancer Detection Demonstration Project (BCDDP), a breast cancer screening program conducted between 1973 and 1980, which was sponsored by the American Cancer Society and the National Cancer Institute (NCI). The BCDDP provided up to five annual breast examinations to 283,222 women at 29 screening centers in 27 cities throughout the United States.[20] The NCI began a separate Follow-up Study of a subset of the BCDDP participants in 1979.

This study recruited a cohort of women defined on the basis of their status at their last BCDDP screening visit. It included four sub-cohorts: (1) all women who were diagnosed with breast cancer (n=4,275); (2) all women who had breast surgery performed during the screening program, with no evidence of malignant breast disease (n=25,114); (3) all women who had received a recommendation by the project for a surgical consultation, but who did not actually have either a biopsy or aspiration performed (n=9,628), and; (4) a sample of women who had not been recommended for surgical consultation and who did not undergo a biopsy (n=25,165). There were a total of 64,182 women from these 4 subgroups who were eligible for participation in the BCDDP Follow-up Study.[21]

The BCDDP Follow-up Study was conducted in four phases. The first phase, carried out between 1979 and 1986, involved the administration of a baseline and up to six annual telephone interviews by the personnel at the BCDDP screening centers. Between 1987 and 1998, phase II (1987-1989), III (1993-1995), and IV (1995-1998) data collections were conducted through self-administered mailed questionnaires to all participants not known to be dead. In addition, attempts were made to conduct follow-up interviews by telephone for all non-respondents to the mailed questionnaires.

Data on race and education were available from screening visits between 1973-1979. Information collected from phase I of the study included age at menarche, number of live births, age at first live birth, ever use of oral contraceptives (if yes: number of years taken and age at first use), age at menopause, ever use of female hormones other than birth control pills (if yes: reasons for use, number of years taken, and age at first use), family

history of breast cancer in specific blood relatives (mother, sister, daughter, grandmother, aunt) including the number in each category affected with breast cancer, menopausal status (including date and reason for periods stopping; menopause was defined as no period having occurred within the three months prior to interview), removal of the uterus and/or ovaries (if yes: year of surgery), and breast biopsy resulting in either benign or malignant diagnoses. Information on all these factors, except for the first four variables (which would be expected to remain constant) was also collected in phases II-IV.

The following information, *not collected during phase I*, was collected during phases II, III, and IV: a more detailed family history of breast cancer, including an enumeration of all first- and second-degree relatives (including half-sisters and both maternal and paternal lineage grandmothers and aunts), the relative's age at breast cancer diagnosis and information regarding whether the breast cancer was unilateral or bilateral; ever use of estrogen and progestin pills in the same month (if yes: age at first use, total duration of use, and number of days in the month progestin pills were taken); medical history, e.g., new cancers (including date of diagnosis); date of first diagnosis of ovarian cancer; tobacco use; physical parameters, including both "usual" and current adult height, weight and body shape.

During each phase, pathology reports were sought for self-reported cancers. In addition, the cohort was linked during each phase to the National Death Index (NDI). Death certificates were retrieved and coded for cause of death during the first three phases of the study. During phase IV, cause of death was obtained from coding done by the NDI.

The cohort was also linked to 19 state cancer registries with the last known address of each participant used as her state of residence.

Analytic cohort

Study population:

Of the 64,182 women selected for participation in the BCDDP Follow-up Study, 61,431 (95.7 percent) completed a baseline interview. Women with a diagnosis of ovarian cancer or who had undergone bilateral oophorectomy *before* the baseline interview were excluded from the analytic cohort, yielding 49,975 women eligible for inclusion in the current analysis. Of the 49,975 eligible women at baseline, 42,068 (84%), 36,623 (73%), and 34,825 (70%) responded to the phase II, III, and IV interviews. Missing phase II questionnaires were due to death (5.0%), illness (0.8%), refusal (3.6%), and inability to contact before the end of the questionnaire period (6.6%). The corresponding proportions for missing phase III and IV questionnaires were 11.0%, 1.0%, 4.0%, and 11.0%; and 15.0%, 1.0%, 1.0%, and 13.0%. In addition, 70.9 percent (n=35,412) of those who answered the baseline interview (n= 49,975) and 73.4 percent (n=30,882) of those who answered the phase II interview (n=42,068) were linked to state cancer registries. Most women in the study were White (87 percent), with small percentages of Black (5 percent), Asian-American (5 percent), and Hispanic (2 percent) participants.

Analytic Data Set

Case definition:

Ovarian cancer cases (ICD_O codes 183.0, 183.3, 183.4, 183.5, 183.8, 183.9, and ICD_9 codes 183.0, 183.3, 183.4, 183.5, 183.8, 183.9, 236.2) were identified through self-report on the follow-up questionnaires (phases II, III, and IV), pathology reports, death certificates, and state cancer registries.

Of the 362 cases identified, 173 were identified by self-report on the follow-up questionnaires; eighty-eight percent of these were confirmed by pathology reports (n=141), state cancer registries (n=4), death certificates only (n=2), or state cancer registries and death certificates (n=6). Independent confirmation was unavailable for 20 self-reports. Five cases were ascertained by pathology reports only, 145 cases were identified by death certificates obtained from the NDI (of these, state cancer registry information provided additional confirmation for 40 cases), and 39 cases were found only by matching study participants to various state cancer registries.

Statistical Analysis

The BCDDP Follow-up Study began upon completion of the baseline interview. In our analysis, person-years accrued until the earliest of the following dates: a) bilateral oophorectomy, b) ovarian cancer diagnosis, c) study end date, which was either the date of completion of the phase IV questionnaire or for non-respondents to phase IV, the date that they would have completed phase IV if still alive, and d) date of death if this date was $\leq$ study end date. To assign dates of cancer diagnosis for cases identified by death certificates only, we used information on the death certificate if 'time since onset of the disease caused death' was specified. Otherwise, other sources such as medical

information from earlier interviews or date of bilateral oophorectomy if the individual had this procedure done, were used. If no additional information was available we used date of death as date of diagnosis.

Time-dependent variables in the analyses included the following: attained age, menopausal status, personal breast cancer diagnosis, duration of oral contraceptive use, duration of estrogen only use, plus all the breast cancer family history variables. Women who reported breast cancer in a sister, mother, and/or daughter were classified as having a "first-degree family history" and those who reported breast cancer in a grandmother, and/or aunt were classified as having a "second-degree family history." Study participants were defined as having a particular family history at their age at the midpoint between first report of exposure and the prior interview. Because information on a family history of ovarian cancer was collected on the last questionnaire, we could not accurately estimate the ages of the study participants at the time their relatives developed ovarian cancer. Thus, family history of ovarian cancer was not considered as a time-dependent variable in the analyses. Analyses that included this variable were restricted to those who answered the phase IV questionnaire.

Rate ratios (RR) and 95 percent confidence intervals (CI) were estimated by Poisson regression.[22] In the final model, RRs were estimated with adjustment for attained age, personal history of breast cancer, and family size. Additional adjustment for sub-cohort did not change the RRs. All the analyses for second-degree family history categories also included adjustments for a first-degree family history. The reference category for all

the analyses comprised women who did not have relatives with breast cancer in that category, as has been done in previously published studies of this kind.

RESULTS

The mean duration of follow-up for study participants was 14.3 years, with a median of 15.9 years, a maximum of 19.8 years, and a minimum of less than one year. During prospective follow-up of the cohort, 715,914 person-years of observation were accumulated for the 49,975 participants. The average age at the start of follow-up was 55 years.

Fifty-four percent of person-years were associated with no breast cancer family history of any type, 31% occurred in women with some family history of breast cancer (i.e., first-degree, second-degree or both), and 15% were associated with an uncertain or unascertained family history. Eighty one percent of accumulated person-years were associated with no first-degree family history of breast cancer, 18% occurred in women with a first-degree family history, and 2% were associated with an uncertain or unascertained first-degree family history; the corresponding percents for a second-degree family history were 64%, 17%, and 19%.

As expected from prior epidemiologic studies, in our study the risk of ovarian cancer was positively associated with attained age, menopausal status, estrogen exposure, family

history of ovarian cancer, and personal history of breast cancer, and was associated inversely with oral contraceptive use (data not shown).

Table 1 summarizes the distribution of person-time for positive- and negative- first-degree family history, according to selected risk factors for ovarian cancer. Person-years associated with a first-degree family history did not vary meaningfully by most factors. A greater percentage of person-years associated with a first-degree family history was evident for older attained age and a personal history of breast cancer.

Rate ratios of ovarian cancer associated with different categories of breast cancer family history are shown in **Table 2**. Since adjustment for attained age and personal history of breast cancer altered these estimates, rate ratios were adjusted for the effects of these factors and a possible confounder, i.e., family size, which were identified as important in most prior familial cancer studies. Additional adjustment for family history of ovarian cancer in the sub-cohort who responded to the phase IV questionnaire didn't affect the relative risk estimates.

In general, women with a breast cancer family history were at increased risk of ovarian cancer when compared to women without a family history of breast cancer in that category. Significant increases in the risk of ovarian cancer were shown among women with any family history of breast cancer, with two or more first-degree relatives with breast cancer, and with any second-degree relative affected. Non-significant increases in risk were also revealed among women with two or more sisters with breast cancer or two

or more daughters with breast cancer. In addition, the rate ratio for women with both a first- and a second-degree relative with breast cancer was elevated, but was not significantly different from unity (RR=1.3, 95% CI=0.76-2.1) (data not shown).

Table 3 presents the rate ratios of ovarian cancer associated with different categories of breast cancer family history among women with a personal history of breast cancer. Non-significant elevated rate ratios were observed among women with a personal history of breast cancer and with any first- or second-degree, and with any first-degree relatives with breast cancer. Women with 2 or more first-degree relatives with breast cancer had a significantly elevated rate ratio of ovarian cancer (RR=3.7, 95% CI=1.8-7.7).

Because both the diagnosis of breast cancer at an earlier than usual age, and the development of cancer in both breasts (i.e., bilateral breast cancer) are considered harbingers of a genetic predisposition to breast cancer, we considered the risk of ovarian cancer taking this information into account. As shown in **Table 4**, there were statistically non-significant increased rates of ovarian cancer among women with affected relatives younger than 50 years of age (RR=1.4, 95% CI=0.87-2.2) or women reporting a bilateral breast cancer in any first-degree relative (RR=1.5, 95% CI=0.72-2.9) when compared to women without a family history of breast cancer in that category. Significantly increased risks were seen among women with 2 or more first-degree affected relatives, at least one of whom had a younger age at breast cancer diagnosis (RR=2.6, 95% CI=1.4-4.8) or bilateral breast cancer (RR=4.2, 95% CI=1.7-10).

In addition, women with a personal history of breast cancer who had a first-degree relative with younger age at breast cancer diagnosis (RR=3.5, 95% CI=1.7-7.4) or bilateral breast cancer (RR=2.6, 95% CI: 0.80-8.7) were at higher risk of ovarian cancer than women with no first-degree family history. Rate ratios associated with a younger age at breast cancer diagnosis or diagnosis of bilateral disease in a first-degree relative was highest among women with both a personal history of breast cancer and with two or more first-degree relatives with breast cancer (RR=6.5, 95% CI=2.7-16; RR=8.3, CI=2.4-28 respectively).

DISCUSSION

In this nationwide prospective study of 49,975 women, reported family history of breast cancer was associated with an increased risk of ovarian cancer, particularly among women with two or more relatives (any relatives and first-degree relatives) with breast cancer. In addition, significantly elevated rate ratios were shown among women with 2 or more first-degree affected relatives, at least one of whom had bilateral breast cancer or younger age (<50) at breast cancer diagnosis. Rate ratios associated with these factors was particularly high among women with a personal history of breast cancer who had 2 or more first-degree affected relatives.

Our results are consistent with most previous case-control and family studies, all of which suggested that having a positive family history of breast cancer increases a woman's risk of developing ovarian cancer.[10-11,15-16,19,23-24] In contrast, one population-

based cohort study found no association between ovarian cancer risk and family history of breast cancer.[25] However, in that study, the family history information was only collected at the baseline interview, the information obtained was much less detailed than the information we obtained, and there were only 18 cases with a family history of breast cancer. These methodological differences may account for the discrepancy between their results and ours.

In addition to our report, two other epidemiologic studies have reported the risk ratios of ovarian cancer for both first- and second-degree relatives of study participants with breast cancer. [16,19] In the study by Ziogas et al., based on a population-based family registry of breast and ovarian cancer, there were excess risks of breast cancer in mothers and sisters of the ovarian cancer probands, but not in grandmothers, aunts, and cousins.[16] In the case-control study by Schildkraut et al., the risk of ovarian cancer conferred by the occurrence of breast cancer in any first-degree relative was elevated (OR=1.5, 95% CI=1.1-2.1), but for breast cancer in second-degree relatives it was 1.2.[19] Although we saw significant excess risks of ovarian cancer among women with one second-degree relative with breast cancer, there was no association between ovarian cancer risk and having two or more second-degree relatives with breast cancer. The small number of cases in this category (n=13) could be responsible for our inability to detect this anticipated association. In addition, the results from the analyses of second-degree relatives could be affected by misclassification of breast cancer history, since it has been shown that reported family history of breast cancer in a second-degree relative is less accurate than a similar history in a first-degree relative.[26-27]

To our knowledge, only one previous study addressed the association between ovarian cancer risk and number of relatives with breast cancer, but there were no conclusive results due to the very small number of cases with more than one relative affected.[19] The occurrence of multiple persons with cancer among the members of a family has numerous possible explanations. These include a shared genetic predisposition, a common environmental exposure, a more complex interaction between genes and environment, and chance. Because our study did not collect information on environmental risk factors from relatives of the participants, we could not differentiate the contribution of shared non-genetic versus genetic factors in the development of ovarian cancer.

Because early age at cancer diagnosis as well as bilaterality in paired organs or multifocality within a single organ are considered the typical features of various hereditary cancer syndromes,[28-31] the significant increases in risk among women with 2 or more first degree relatives, at least one of whom had bilateral breast cancer or younger age (<50) at breast cancer diagnosis in our study are consistent with the hypothesis that shared genetic pathways are involved in the etiology of at least some ovarian and breast cancer cases. Only a few studies have addressed the association between ovarian cancer risk and family history of breast cancer with respect to relatives' age at breast cancer diagnosis. In a case-control study by Schildkraut et al. (1989), it was reported that early age (<45) at onset of breast cancer among mothers and sisters was associated with an increased risk of ovarian cancer in probands.[10] A cohort study of breast cancer mortality in mothers and sisters of women with ovarian cancer showed non-significant excesses for

age groups of <40, 50-59, and 70-79 years.[14] In contrast, an analysis of 319 pedigrees of ovarian cancer patients with a first-degree relative with ovarian cancer showed a significant excess risk of breast cancer with an older age at diagnosis (≥50) among first-degree relatives.[12]

The hereditary breast ovarian cancer syndrome (HBOC) is an established genetic disorder that predisposes to both ovarian and breast cancers among members of the same family.[5,10,32-33] It is in this setting that the association between early age at breast cancer diagnosis and the presence of bilateral breast cancer has been most clearly linked to hereditary breast and ovarian cancer susceptibility. In addition, one of the most potent predictors of the likelihood of identifying a BRCA1 or BRCA2 mutation in a high-risk family is the presence of a family member with separate primary cancers of ***both*** the breast and the ovary.[34-35] The fact that women in the BCDDP Follow-up Cohort with a personal history of breast cancer displayed a 1.5-fold increase in the risk of ovarian cancer (95% CI: 1.1-2.0) provides additional support for the hypothesis that one component of the association between breast and ovarian cancer described herein is a true genetic predisposition. Further support is provided by the observation that in this study, women with a personal history of breast cancer had 3.5 and 2.6 fold excess risks of ovarian cancer if they had a first-degree relative with an early age at breast cancer diagnosis and bilateral breast cancer, respectively. Moreover, women with a personal history of breast cancer and with 2 or more first-degree affected relatives, at least one of whom had bilateral breast cancer or younger age at breast cancer diagnosis, had still higher risks.

Ovarian cancer is one of the extra-colonic malignancies that occurs excessively in persons with hereditary nonpolyposis colorectal cancer (HNPCC).[36-37] The estimated risk of ovarian cancer to age 70 in women with mutations in one of the mismatch repair genes is approximately 9%,[38] compared with 1.4% in the general population.[39] It has been suggested by some (but not all) investigators that HNPCC may also include a predisposition to breast cancers among members of the same family.[40-41] Because we had incomplete data on family history of cancers other than breast, we were unable to determine whether any of the association between breast and ovarian cancer in our study might be attributable to the presence of women with this syndrome.

Several methodologic issues need to be considered in interpreting our results. Although we had incomplete information on a family history of ovarian cancer, adjustment for this variable did not alter our results in the sub-cohort of women who provided information on this variable (data not shown). In addition, in a case-control study by Parazzini et al., the adjusted and unadjusted odds ratios of ovarian cancer for a family history of ovarian cancer were similar.[11] This lack of confounding by the ovarian cancer family history could be due to the fact that ovarian cancer is a rare outcome,[42] and that family history of breast cancer can be as strong a predictor of risk as family history of ovarian cancer. If we had systematically collected data on a family history of ovarian cancer throughout the study, we likely would have been better able to classify women with respect to potentially inherited susceptibility to BRCA genes.

Although we attempted to maximize ascertainment of ovarian cancer cases by identifying cases through the National Death Index (death certificates), pathology reports, and by

means of linkage to state cancer registries for study participants who had died, who failed to answer all questionnaires, or who became lost to follow-up, there is undoubtedly some under-ascertainment of ovarian cancer cases in this cohort. However, the loss to follow-up and potential under-ascertainment of cases did not vary by family history of breast cancer and thus was not likely to bias our rate ratio estimates.

Our study is also subject to the possibility of recall bias. Some of the information on family history of breast cancer was obtained prospectively, but some was obtained after the diagnosis of ovarian cancer. However, a methodological study found no difference in the reporting of breast cancer in family members between patients with and without breast cancer.[43] It is likely that this study would also be applicable to ovarian cancer cases reporting a family history of breast cancer.

Third, no attempt was made to obtain objective verification of the breast cancers that were reported by study participants to have occurred among their relatives. However, prior studies have shown that the accuracy of reported occurrences of breast cancer in family studies is very high, in the range of 83%-95%,[26,43-46] family history report of breast cancer in a second-degree relative is somewhat less accurate.[26-27] We are therefore reasonably confident regarding the reliability of the reported family history information, particularly among first-degree relatives.

In summary, our cohort study found an association between family history of breast cancer and ovarian cancer risk, which varied with the number of first-degree relatives

affected, the age at breast cancer diagnosis, and whether the cancer was bilateral. Considering the typical features of various hereditary cancer syndromes: 1) early age of onset, 2) high incidence of multiple persons with cancer among family members, and 3) bilaterality in paired organs, the observed associations in our study support the hypothesis that shared genetic pathways are involved in the etiology of at least some ovarian and breast cancer cases, and that this familial risk factor (most likely genetic) is sufficiently strong that it can be detected in the general population setting when an appropriately detailed family history is taken. Clinicians who are caring for women with ovarian cancer may find it useful to consider carefully the details of breast cancer occurrence among their patients' relatives, as they search for that subset of patients with ovarian cancer upon which a more detailed genetic risk assessment might be focused.

ACKNOWLEDGEMENT

We thank the BCDDP participants; Susan Englehart, Catherine Ann Grundmayer, and the members of the BCDDP Staff at Westat Inc, Rockville, MD; and Leslie Carroll, Franklin Demuth, Jennifer Boyd-Morin, and David Campbell, Jr. of IMS Inc, Silver Spring, MD, for computer support. We acknowledge the California Department of Health Services, Cancer Surveillance Section; Florida Cancer Data System, under contract to the Florida Department of Health; Maryland Cancer Registry, Maryland Department of Health and Mental Hygiene; Michigan Cancer Surveillance Program within the Division of Vital Records and Health Statistics, Michigan Department of Community Health; Pennsylvania Department of Health; Tennessee Cancer Registry; Texas Department of Health; and the states of Arizona, Georgia, Hawaii, Idaho, Iowa, New Jersey, New York, North Carolina,

Ohio, Oregon, and Rhode Island for providing data from their cancer registries for use in these analyses. The opinions or assertions contained in this manuscript are the personal conclusions of the authors and are not to be construed as official or reflecting the views of any state agency listed above, the United States Department of Defense, or the Uniformed Services University of the Health Sciences.

REFERENCES

1. American Cancer Society. Cancer Facts & Figures. American Cancer Society, Inc. Atlanta, GA. 2002

2. Parazzini F, Franceschi S, La Vecchia C, et al: The epidemiology of ovarian cancer. Gynecol Oncol 43:9-23, 1991

3. Vasen HF, Wijnen JT, Menko FH, et al: Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. Gastroenterology 110:1020-7, 1996

4. Ford D, Easton DF, Stratton M, et al: Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet 62:676-89, 1998

5. Go RC, King MC, Bailey-Wilson J, et al: Genetic epidemiology of breast cancer and associated cancers in high-risk families. I. Segregation analysis. J Natl Cancer Inst 71:455-61, 1983

6. Miki Y, Swensen J, Shattuck-Eidens D, et al: A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 266:66-71, 1994

7. Tavtigian SV, Simard J, Rommens J, Couch F, Shattuck-Eidens D, Neuhausen S et al. The complete BRCA2 gene and mutations in chromosome 13q-linked kindreds. Nat Genet 12:333-7, 1996

8. Narod SA, Ford D, Devilee P, et al: An evaluation of genetic heterogeneity in 145 breast-ovarian cancer families. Breast Cancer Linkage Consortium. Am J Hum Genet 56:254-64, 1995

9. Boyd J. Molecular genetics of hereditary ovarian cancer. Oncology (Huntingt) 12:399-406, 1998

10. Schildkraut JM, Risch N, Thompson WD. Evaluating genetic association among ovarian, breast, and endometrial cancer: Evidence for a breast/ovarian cancer relationship. Am J Hum Genet 45:521-9, 1989

11. Parazzini F, Negri E, La Vecchia C, et al: Family history of reproductive cancers and ovarian cancer risk: an Italian case-control study. Am J Epidemiol 135:35-40, 1992

12. Houlston RS, Bourne TH, Collins WP, et al: Risk of ovarian cancer and genetic relationship to other cancers in families. Hum Hered 43:111-5, 1993

13. Kerber RA, Slattery ML. The impact of family history on ovarian cancer risk. The Utah Population Database. Arch Intern Med 155:905-12, 1995

14. Easton DF, Matthews FE, Ford D, et al: Cancer mortality in relatives of women with ovarian cancer: the OPCS Study. Office of Population Censuses and Surveys. Int J Cancer 65:284-94, 1996

15. Poole CA, Byers T, Calle EE, et al: Influence of a family history of cancer within and across multiple sites on patterns of cancer mortality risk for women. Am J Epidemiol 149:454-62, 1999.

16. Ziogas A, Gildea M, Cohen P, et al: Cancer risk estimates for family members of a population-based family registry for breast and ovarian cancer. Cancer Epidemiol Biomarkers Prev 9:103-11, 2000

17. Thompson WD, Schildkraut JM. Family history of gynaecological cancers: relationships to the incidence of breast cancer prior to age 55. Int J Epidemiol 1991;20:595-602, 1991

18. Peto J, Easton DF, Matthews FE, et al: Cancer mortality in relatives of women with breast cancer: the OPCS Study. Office of Population Censuses and Surveys. Int J Cancer 65:275-83, 1996

19. Schildkraut JM, Thompson WD. Relationship of epithelial ovarian cancer to other malignancies within families. Genet Epidemiol 5:355-67, 1988

20. Baker LH. Breast Cancer Detection Demonstration Project: five-year summary report. CA Cancer J Clin 32:194-225, 1982

21. Schairer C, Lubin J, Troisi R, et al: Estrogen-progestin replacement and risk of breast cancer. JAMA 284:691-4, 2000

22. Breslow NE, Day NE: "Statistical Methods in Cancer Research: Vol II. The Design and Analysis of Cohort Studies." Lyon: International Agency for Research on Cancer, IARC Scientific Publications No. 82:131-35,160-67,185, 1987

23. Cramer DW, Hutchison GB, Welch WR, et al: Determinants of ovarian cancer risk. I. Reproductive experiences and family history. J Natl Cancer Inst 71:711-6, 1983

24. Kerber RA, Slattery ML. The impact of family history on ovarian cancer risk. The Utah Population Database. Arch Intern Med 1995;155(9):905-12.

25. Nelson CL, Sellers TA, Rich SS, et al: Familial clustering of colon, breast, uterine, and ovarian cancers as assessed by family history. Genet Epidemiol 10:235-44, 1993

26. Love RR, Evans AM, Josten DM. The accuracy of patient reports of a family history of cancer. J Chronic Dis 38:289-93, 1985

27. Theis B, Boyd N, Lockwood G, Tritchler D. Accuracy of family cancer history in breast cancer patients. Eur J Cancer Prev 3:321-7, 1994

28. Knudson AG. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA 68:820-823, 1971

29. Anderson DE. Breast cancer in families. Cancer 40:1855-1860, 1977

30. Verhoog LC, Brekelmans CT, Seynaeve C, et al: Survival and tumour characteristics of breast-cancer patients with germline mutations of BRCA1. Lancet 351:316-21, 1998

31. Robson M, Gilewski T, Haas B, et al: BRCA-associated breast cancer in young women. J Clin Oncol 16:1642-9, 1998

32. Lynch HT, Harris RE, Guirgis HA, et al: Familial association of breast/ovarian carcinoma. Cancer 41:1543-1549, 1978

33. Piver MS, Mettlin CJ, Tsukada Y, et al: Familial ovarian cancer registry. Obstet Gynecol 64:195-199, 1984

34. Fishman A, Dekel E, Chetrit A, et al: Patients with double primary tumors in the breast and ovary- clinical characteristics and BRCA1-2 mutations status. Gynecol Oncol 79:74-8, 2000

35. Shih HA, Nathanson KL, Seal S, et al: BRCA1 and BRCA2 mutations in breast cancer families with multiple primary cancers. Clin Cancer Res 6:4259-64, 2000

36. Bewtra C, Watson P, Conway T, et al: Hereditary ovarian cancer: A clinicopathological study. Int J Gynecol Pathol 11:180-187, 1992

37. Watson P, Lynch HT. Extracolonic cancer in hereditary nonpolyposis colorectal cancer. Cancer 71:677-85, 1993

38. Aarnio M, Mecklin JP, Aaltonen LA, et al: Life-time risk of different cancers in hereditary non-polyposis colorectal cancer (HNPCC) syndrome. Int J Cancer 64:430-3, 1995

39. Parkin D, Muir C, Whelan SL, et al: Cancer Incidence in Five Continents. IARC Scientific Publications VII:1018-9, 1997

40. Risinger JI, Barrett JC, Watson P, et al: Molecular genetic evidence of the occurrence of breast cancer as an integral tumor in patients with the hereditary nonpolyposis colorectal carcinoma syndrome. Cancer 77:1836-1843, 1996

41. Scott RJ, McPhillips M, Meldrum CJ, et al: Hereditary nonpolyposis colorectal cancer in 95 families: differences and similarities between mutation-positive and mutation-negative kindreds. Am J Hum Genet 68:118-127, 2001

42. Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Edwards BK. Eds. SEER Cancer Statistics Review, 1973-1998. National Cancer Institute, NIH, Bethesda, MD. 2001.

43. Parent ME, Ghadirian P, Lacroix A, et al: The reliability of recollections of family history: implications for the medical provider. J Cancer Educ 12:114-20, 1997

44. Kerber RA, Slattery ML. Comparison of self-reported and database-linked family history of cancer data in a case-control study. Am J Epidemiol 146:244-8, 1997

45. Eerola H, Blomqvist C, Pukkala E, et al: Familial breast cancer in southern Finland: how prevalent are breast cancer families and can we trust the family history reported by patients? Eur J Cancer 36:1143-8, 2000

46. Douglas FS, O'Dair LC, Robinson M, et al: The accuracy of diagnoses as reported in families with cancer: a retrospective study. J Med Genet 36:309-12, 1999

Table 1. Percentage of person-years associated with a first-degree family history of breast cancer according to selected factors in BCDDP ovarian cancer Follow-up Study, 1979-1998

Risk factor	Negative 1st degree family history of breast cancer (%)	Positive 1st degree family history of breast cancer (%)	Unsure 1st degree family history of breast cancer (%)	Total person-years
Attained age (yrs)				
<50	85.3	13.7	1.0	63,176
50-54	83.1	15.3	1.6	98,312
55-59	81.5	16.6	1.9	138,368
60-64	80.1	17.9	2.1	140,050
65-69	78.6	19.2	2.2	114,298
70-74	77.1	20.6	2.3	78,548
75+	75.1	22.4	2.5	83,161
Menopausal status				
Pre-menopause	80.6	17.5	1.9	249,232
Menopause	79.8	18.2	2.0	450,580
Unknown	80.0	17.2	2.8	16,102
Personal history of breast cancer				
Never	81.1	17.0	1.9	647,592
Ever	70.9	26.7	2.4	68,321
Duration of oral contraceptive use				
No use	79.8	18.2	2.0	503,132
<3	80.7	17.5	1.8	105,796
3-<9	80.6	17.6	1.8	69,198
≥9	81.8	16.2	2.0	32,203
Unknown	81.9	14.5	3.6	5,585
Duration of estrogen only use (yrs)				
No use	80.5	17.8	1.7	344,158
<8	80.9	17.3	1.8	136,839
8-<16	78.7	19.1	2.2	33,475
≥16	78.8	19.2	2.0	19,087
Unknown	78.9	18.9	2.2	30,901

Table 2. Rate ratios (RR) of ovarian cancer associated with family history of breast cancer in BCDDP ovarian cancer Follow-up Study, 1979-1998

Relative	No. of Person-Years	No. of Cases	Adjusted * RR (95% CI)
Any family history			
No history	385,566	177	1.0 (reference)
1 affected	155,669	90	1.3 (1.0-1.7)
2 or more affected	64,851	40	1.4 (1.0-2.0)
Any affected	220,520	130	1.4 (1.1-1.7)
Unknown	109,828	55	1.1 (0.8-1.5)
Any 1st degree			
No history	573,387	279	1.0 (reference)
1 affected	109,251	55	1.0 (0.8-1.4)
2 or more affected	19,190	19	1.8 (1.1-2.8)
Any affected	128,441	74	1.1 (0.9-1.5)
Unknown	14,086	9	1.2 (0.6-2.3)
Mother			
No history	633,392	314	1.0 (reference)
Mother affected	69,519	39	1.2 (0.8-1.6)
Unknown	13,003	9	1.3 (0.7-2.5)
Sister			
No history	642,969	314	1.0 (reference)
1 affected	54,773	33	1.1 (0.8-1.6)
2 or more affected	9,214	9	1.7 (0.9-3.3)
Any affected	63,987	42	1.2 (0.9-1.7)
Unknown	8,958	6	1.2 (0.5-2.7)
Daughter			
No history	702,808	350	1.0 (reference)
1 affected	5,081	4	1.3 (0.5-3.5)
2 or more affected	701	2	4.6 (1.1-19)
Any affected	5,782	6	1.7 (0.7-3.8)
Unknown	7,324	6	1.6 (0.7-3.5)
Any 2nd degree			
No history	455,025	214	1.0 (reference)
1 affected	96,212	61	1.4 (1.1-1.9)
2 or more affected	29,105	13	1.0 (0.6-1.7)
Any affected	125,317	74	1.3 (1.0-1.7)
Unknown	135,571	74	1.0 (0.8-1.3)

Table 2. Rate ratios (RR) of ovarian cancer associated with family history of breast cancer in BCDDP ovarian cancer Follow-up Study, 1979-1998

Relative	No. of Person-Years	No. of Cases	Adjusted * RR (95% CI)
Grand mother			
No history	563,301	272	1.0 (reference)
1 affected	29,988	18	1.3 (0.8-2.1)
2 affected	1,663	1	1.2 (0.2-8.3)
Any affected	31,651	19	1.3 (0.8-2.0)
Unknown	120,962	71	1.0 (0.8-1.3)
Aunt			
No aunt's history	514,886	252	1.0 (reference)
1 affected	82,795	48	1.2 (0.9-1.7)
2 or more affected	20,037	9	0.9 (0.5-1.8)
Any affected	102,832	57	1.2 (0.9-1.6)
Unknown	98,196	53	0.9 (0.7-1.3)

*Adjusted for number of relatives, attained age, and breast cancer diagnosis. The second-degree variables were also adjusted for a 1st degree family history. Women who did not have relatives with breast cancer in that category formed the reference group for each group.

Table 3. Rate ratios (RR) of ovarian cancer associated with family history of breast cancer among women with a personal history of breast cancer in BCDDP ovarian cancer Follow-up Study, 1979-1998

Relative	No. of Person-Years	No. of Cases	Adjusted * RR (95% CI)
Any family history			
No history	30,811	24	1.0 (reference)
1 affected	17,730	12	1.0 (0.5-2.0)
2 or more affected	9,539	13	1.9 (1.0-3.9)
Any affected	27,269	25	1.3 (0.7-2.4)
Unknown	10,241	6	0.8 (0.3-2.1)
Any 1st degree			
No history	48,420	34	1.0 (reference)
1 affected	14,556	11	1.2 (0.6-2.3)
2 or more affected	3,714	10	3.7 (1.8-7.7)
Any affected	18,270	21	1.7 (1.0-2.9)
Unknown	1,631	0	---
Any 2nd degree			
No history	40,095	32	1.0 (reference)
1 affected	10,556	7	0.9 (0.4-2.1)
2 or more affected	3,659	3	1.0 (0.3-3.5)
Any affected	14,215	10	0.9 (0.4-2.0)
Unknown	14,010	13	1.4 (0.7-3.0)

*Adjusted for number of relatives, and attained age. The second-degree variables were also adjusted for a 1st degree family history.
Women who did not have relatives with breast cancer in that category formed the reference group for each group.

Table 4. Rate ratios for ovarian cancer, 95% Confidence Intervals, number of cases and total person-years by age of diagnosis and disease laterality of relative with breast cancer

	First-Degree Relative					
	Age at Diagnosis*			Laterality Status		
Reference Group	<50	≥50	Unknown	Unilateral	Bilateral	Unknown
1.0	1.4	0.8	1.5	0.7	1.5	1.4
	(0.9-2.2)	(0.5-1.2)	(1.0-2.2)	(0.5-1.1)	(0.7-2.9)	(1.0-2.0)
CA/PY	20/32,762	24/64,063	30/31,162	20/60,124	8/12,154	47/57,333
Women with 2 or more first-degree relatives with breast cancer[φ]						
1.0	2.6	1.3	0.9	1.4	4.2	1.4
	(1.4-4.8)	(0.6-3.1)	(0.2-3.5)	(0.6-3.5)	(1.7-10)	(0.7-2.7)
CA/PY	11/8,072	6/7,670	2/3,350	5/6,026	5/2,136	9/11,020
Women with a personal history of breast cancer						
1.0	3.5	0.7	1.8	1.2	2.6	1.7
	(1.7-7.4)	(0.3-2.0)	(0.8-4.2)	(0.5-2.9)	(0.8-8.7)	(0.9-3.4)
CA/PY	10/4,484	4/9,387	7/4,303	6/8,206	3/1,870	11/8,253
Women with a personal history of breast cancer and with 2 or more first-degree relatives with BC[φ]						
1.0	6.5	2.8	--	3.6	8.3	2.4
	(2.7-16)	(0.8-9.4)		(1.1-12)	(2.4-28)	(0.9-7.0)
CA/PY	7/1,574	3/1,559		3/1,131	3/476	4/2,104

*Age at diagnosis is the age of youngest relative in that category with breast cancer.
All analyses are adjusted for attained age, number of first-degree relatives, and personal breast cancer diagnosis (the analyses among women with a personal history of breast cancer did not include this variable).
[φ] At least one of whom had the age at diagnosis or laterality characteristic.
Women who did not have first-degree relatives with breast cancer formed the reference category for each group. If women with a personal history of breast cancer formed a group, the reference category also included women with this characteristic.
CA= Number of cases; PY= Total person-years.

Family History of Breast Cancer as a Determinant of the Risk of Developing Endometrial and Ovarian Cancers: A Nationwide Cohort Study

DISCUSSION

OVERALL DISCUSSION

Our study is the first large prospective cohort study to evaluate the risk of developing either endometrial or ovarian cancer in relation to an extensive breast cancer family history data. These familial breast cancer data include:

- Periodic updates of family history information on several occasions during the course of follow-up;
- Information on the occurrence of breast cancer in both first- and second-degree relatives of study participants;
- Enumeration of total numbers of first- and second-degree female relatives, allowing the analysis to be adjusted for family size; and
- Data regarding the age of breast cancer diagnosis, and laterality, for relatives who were reported with breast cancer during the course of prospective follow-up.

We found that family history of breast cancer was not associated with an increased risk of endometrial cancer, but it was associated with an increased risk of ovarian cancer, particularly among women with two or more affected first-degree relatives. In addition, significantly elevated rate ratios for ovarian cancer were shown among women with 2 or more first-degree affected relatives, at least one of whom had bilateral breast cancer or younger age (<50) at breast cancer diagnosis. Risk associated with these factors was particularly high among women with a personal history of breast cancer who also reported 2 or more first-degree affected relatives.

In considering these results, the following features of our studies are considered as the strengths in this report:

- High response rates for each phase of the study, i.e., aggressive, comprehensive efforts at follow-up, as indicated in the manuscripts and Methods Chapter, kept the proportion of participants lost to follow-up to a minimum.
- Use of ancillary methods for case ascertainment that were employed in this study made it possible to capture ovarian/endometrial cancer cases that would have been missed had only a single mode of ascertainment been used. This improved the statistical power of our analyses to detect an association and increased the power of our study to generalize the results to the entire population of women with ovarian/endometrial cancer, rather than the selected subset which would have been found with a less comprehensive approach to case-finding;
- Periodic updates of family history information on several occasions during the course of follow-up allowed a more accurate classification of the participants with regard to their exposure status. This approach minimized the possibility of exposure misclassification in our study; and
- Periodic updates of information on other risk factors related to the cancer endpoints of interest were obtained on several occasions during the course of follow-up, thus permitting adjustments for these risk factors as time-dependent variables.

Discussion of the Endometrial Cancer Follow-up Study Results

Our analysis of breast cancer family history as a risk factor for the development of endometrial cancer yielded a null result. The hypothesis had its basis in a series of

observations suggesting that endometrial cancer and breast cancer shared an important set of risk factors, i.e., nulliparity, and exposure to unopposed estrogen. Furthermore, as discussed in the Introduction Chapter, a variety of data were consistent with the possibility that a family history of breast cancer might increase the risk of endometrial cancer.

The results in Appendix B (Table 1) provide significant reassurance regarding the biologic integrity of this cohort of women. When we analyzed the relationship between the prospective development of endometrial cancer and previously established endometrial cancer risk factors in this study, the findings were remarkably consistent with what is already known about the etiology of this cancer (Mac Mahon, 1974; Hoover et al, 1976; Kelsey et al, 1982; La Vecchia et al, 1984; Kvale et al, 1991; Brinton et al, 1992; Austin et al, 1993; Weiderpass et al, 2000).

It is also reassuring that the results from the endometrial cancer Follow-up Study are consistent with the reports of two other, previously published, large cohort studies, making it unlikely that our results represent a false negative finding (Olson et al., 1999; Nelson et al., 1993). Our novel time-dependent analytic approach yielded the same results as in these two cohort studies, in which the family history data were collected only at baseline.

However, our results are inconsistent with a family study of high-risk families with breast cancer (Lynch et al., 1972). One possible explanation for this discrepancy is that if there are shared genetic components playing a role in endometrial and breast cancer pathogenesis, these factors may be detectable only among highly selected families with

an inherited cancer susceptibility, and that such effects are not common enough to be detected at the population level.

Another possible explanation for the null results in our endometrial cancer analysis and the other two endometrial cancer cohort studies (Olson et al., 1999; Nelson et al., 1993) derive from the age structure of the populations under study, as was discussed in our endometrial cancer manuscript. It is possible that women with a hereditary predisposition to endometrial cancer, who tend to be diagnosed at earlier age, might have died or have developed endometrial cancer before the start of the Follow-up Study in 1979.

Finally, of course, it may be correct that family history of breast cancer is **not** a risk factor for endometrial cancer. Even though the hypothesis we set out to test was a plausible one, the overall strength of the prior evidence was modest. The existing evidence certainly would not have justified undertaking a study of this magnitude to test specifically this particular hypothesis. We performed this analysis because the previously established cohort permitted us to do so at minimal additional cost, and because the scientific question was an interesting if not a compelling one. Thus, it may not be surprising that we failed to detect the proposed association. The large size of the overall cohort, the large number of prospectively diagnosed endometrial cancers, the availability of comprehensive endometrial cancer risk factor information, and the unusually detailed breast cancer family history information combine to make this a strong negative study. Most convincingly, the pattern of positive associations detected in the companion ovarian cancer analysis provides considerable support for our belief that the findings related to endometrial cancer are correct.

Discussion of the Ovarian Cancer Follow-up Study Results

Our results with regard to the hypothesized association between ovarian cancer risk and family history of breast cancer yielded significant associations. Reported family history of breast cancer was associated with an increased risk of ovarian cancer, particularly among women with two or more relatives (any relatives and first-degree relatives) with breast cancer. In addition, significantly elevated rate ratios were shown among women with 2 or more first-degree affected relatives, at least one of whom had bilateral breast cancer or younger age (<50) at breast cancer diagnosis. Risk associated with these factors was particularly high among women with a personal history of breast cancer and with 2 or more first-degree affected relatives.

The occurrence of multiple persons with cancer among the members of a family has numerous possible explanations. These include a shared genetic predisposition, a common environmental exposure, a more complex interaction between genes and environment, and chance. Because the BCDDP Follow-up Study did not collect information on environmental risk factors from relatives of the participants, we could not evaluate the contribution of shared non-genetic factors in the development of ovarian cancer. However, simulation studies have shown that even despite high correlations in environmental exposures among family members, the relative risks of the disease associated with these factors must be on the order of ten-fold to yield increases in the disease risk among family members (Khoury et al., 1988; Hopper and Carlin, 1992). The ovarian cancer risk associated with the majority of environmental risk factors have been on the order of two-fold or less. Therefore, it seems unlikely that familial clustering of these factors could entirely explain the observed association in our study.

In addition, considering the fact that early age at cancer diagnosis as well as bilaterality in paired organs or multifocality within a single organ are considered the typical features of various hereditary cancer syndromes (Knudson, 1971; Anderson, 1977; Verhoog, et al., 1998; Robson et al., 1998), our observed associations are consistent with the hypothesis that perhaps shared genetic pathways are involved in the etiology of at least some ovarian and breast cancer cases.

The hereditary breast ovarian cancer syndrome (HBOC) is an established genetic disorder that predisposes to both ovarian and breast cancers among members of the same family (Lynch et al., 1978; Go et al., 1983; Piver et al., 1984; Schildkraut et al., 1989). The majority of HBOC syndrome families are linked to the breast cancer susceptibility genes BRCA1 and BRCA2 (Hall et al., 1990; Miki et al., 1994; Wooster et al., 1995). It is in this setting that the association between early age at breast cancer diagnosis and the presence of bilateral breast cancer has been most clearly linked to hereditary breast and ovarian cancer susceptibility.

In addition, one of the most potent predictors of the likelihood of identifying a BRCA1 or BRCA2 mutation in a high-risk family is the presence of a family member with separate primary cancers of ***both*** the breast and the ovary (Fishman et al., 2000; Shih et al., 2000). Lynch et al., (1999) have reported that in addition to an increased risk of ovarian cancer, women who carry BRCA1 mutations have an increased incidence of bilateral breast cancer with a second primary breast cancer occurring in 40% to 60% of patients. Additionally, Frank et al. (1998) reported that women with breast cancer who carry mutations in BRCA1 or BRCA2 have a ten-fold increase in the risk of subsequent ovarian cancer compared with women without mutations. The fact that women in the

BCDDP Follow-up Study with a personal history of breast cancer displayed a 1.5-fold increase in the risk of ovarian cancer (95% CI: 1.1-2.0) provides additional support for the hypothesis that one component of the association between breast and ovarian cancer described herein is a true genetic predisposition. Further support is provided by the observation that in this study, women with a personal history of breast cancer had 3.5 and 2.6 fold excess risks of ovarian cancer if they had a first-degree relative with an early age at breast cancer diagnosis and bilateral breast cancer, respectively. Moreover, women with a personal history of breast cancer and with 2 or more first-degree affected relatives, at least one of whom had bilateral breast cancer or younger age at breast cancer diagnosis, had significantly higher risks. Together, this set of findings is quite consistent with what was known previously about the familial occurrence of breast and ovarian cancer. Our report is distinctive, however, in having been able to demonstrate this pattern in a cohort of women that approximates the general population.

Methodologic Considerations and Limitations

Several methodologic issues need to be considered in interpreting our results. We attempted to maximize ascertainment of endometrial or ovarian cancer cases by identifying cases through the National Death Index (death certificates), pathology reports, and by means of linkage to state cancer registries for all study participants. In spite of these efforts, there is undoubtedly some under-ascertainment of endometrial or ovarian cancer cases in the BCDDP Follow-up Study. For example, not every state has a population-based cancer registry against which the members of our cohort could be matched. The BCDDP cancer linkage records were sent to 27 state cancer registries, and

we were able to link our data to 19 states due to the restrictions imposed by some cancer registries. If a cohort member died in one of the states lacking a registry or where the data could not be linked, and this person had failed to notify the study team of their having developed a new endometrial or ovarian cancer, such cases would be missed if they didn't die of the cancer.

A biased rate ratio could result if under-ascertainment of cases were related to the "exposure" being investigated, i.e., to the family history of breast cancer. The difference in response to the phase II, III, and IV questionnaires between participants with and without a first-degree family history of breast cancer at the baseline was one percentage point for phases II (84 percent and 85 percent, respectively), III (73 and 74 percent), and IV (70 and 69 percent). To affect the estimate of the true relative risk meaningfully, the proportion of cases ascertained in the exposed and unexposed groups would have to differ appreciably or be small percentages of all cases, including the cases that could not be ascertained, in each group.

Non-differential misclassification of exposure (i.e., a positive family history of breast cancer) would bias estimates of the rate ratio toward the null value. Several sources of misclassification of exposure should be considered in this study:

1) Because of the gaps between questionnaires (i.e., a 6-year gap between phase II and phase III, and a 3-year gap between phase III and phase IV), we had to estimate the age of the respondent at the time a positive family history first developed. Family history of breast cancer was handled as a time-dependent variable in the current analysis for both the cases and non-cases. Age at the time family history status changed was defined as the midpoint between the first report

of exposure and the prior interview. This should lead to a non-differential misclassification of exposure;

2) Our study is also subject to the possibility of recall bias. Some of the information on family history of breast cancer was obtained prospectively, but some was obtained after diagnosis of endometrial or ovarian cancer. However, a methodological study found no difference in the reporting of breast cancer in family members between women with and without breast cancer (Parent et al., 1997). It is unlikely recall would differ between women with and without breast, ovarian, or endometrial cancer.

3) In addition, in our study, no attempt was made to obtain objective verification of the breast cancers that were reported by study participants to have occurred among their relatives. However, prior studies have shown that the accuracy of reported occurrences of breast cancer in family studies, is very high, in the range of 83%-95% (Eerola et al., 2000; Douglas et al. 1999; Kerber and Slattery, 1997; Parent et al., 1997; Love et al. 1985); family history report of breast cancer in a second-degree relative is somewhat less accurate (Love et al., 1985; Theis et al., 1994). We are therefore only reasonably confident regarding the reliability of the reported second-degree family history information.

4) With regard to age at relative's diagnosis and unilateral versus bilateral breast disease, the prior literature on the accuracy of breast cancer family history did not assess the validity of such data. Also, we were not able to estimate the false-negative rates (i.e., the frequency with which a respondent reported a negative

family history when, in fact, the family history was positive) and thus we could not account for this in our analyses.

One of the limitations of the family history data in our study is the fact that up through phase III, information was sought *only for family history of breast cancer*. This made it impossible to assess whether any of the endometrial or ovarian cancer cases in our study occurred in families likely to be affected by other familial cancer syndromes. For example, endometrial and ovarian cancer are among the extra-colonic malignancies that occur excessively in persons with hereditary nonpolyposis colorectal cancer (HNPCC) (Watson and Lynch, 1993; Hakala et al., 1991; Bewtra et al., 1992). This syndrome may also include a predisposition to breast cancer among members of the same family (Risinger et al., 1996; Scott et al., 2001). Thus, it would be of interest to consider whether any of the association between ovarian and breast cancer seen in the present study might be attributable to the presence of women from families with a pattern of cancers suggestive of HNPCC. Unfortunately, we were unable to investigate this in the entire cohort because no information was available regarding reported history of colorectal cancer among the relatives of study participants before phase IV. However, we conducted an analysis of the association between ovarian cancer risk and first-degree family history of colorectal cancer, using the limited data available from the phase IV questionnaire and found no association (Appendix B, Table 13).

Although slightly more than half of our study participants were women with either a breast cancer diagnosis or a history of benign breast disease, our study results still seem to be pertinent to the general population. These existing breast conditions did not confound the estimates of risk in our studies. Adjustment for prior breast cancer

diagnosis or breast disease in both studies had no effect on the results. Additionally, all of our analyses were adjusted for the effect of personal history of breast cancer.

Conclusions

In summary, we found no overall association between a family history of breast cancer and endometrial cancer risk, but did find an association between a family history of breast cancer and ovarian cancer risk, which varied with the number of relatives affected, the age at breast cancer diagnosis, and whether the breast cancer was bilateral. Considering the typical features of various hereditary cancer syndromes: 1) early age of onset; 2) high incidence of multiple persons with cancer among family members, and 3) bilaterality in paired organs, these observed associations in our study support the hypothesis that shared genetic pathways are involved in the etiology of at least some ovarian and breast cancer cases and that the familial risk factor is sufficiently strong that it can be detected in the general population setting when an appropriately detailed family history is taken.

The most important consequence of our observations is the demonstration that a carefully taken family history in a cohort of women that approximates the general population can detect the clinical clues which would permit a thoughtful clinician to identify among all their patients with ovarian cancer that subset upon which a more detailed genetic risk assessment might be focused. The women in our study were not recruited because of dramatic family histories, nor were they ascertained through the highly selected mechanism of attendance at a high-risk clinic. The subjects in the current analysis resemble the majority of women who seek day-to-day medical attention from

their various health care providers. Even in this setting, it appears that it is possible to identify persons with family history features suggestive of a familial or an inherited disorder. Thus, even in the modern era of molecular biology, there remains an essential role for a careful family history in the management of women with ovarian cancer.

Public Health Implications and Directions

Detecting a family history of cancer during the course of a clinical evaluation requires consideration of genetic, environmental, and behavioral contributions to that family's cancer susceptibility. The family history information can be used in the public health settings and the practice of preventive medicine to assess individual cancer risk. This may permit development and assessment of early detection and prevention strategies at both the population and individual level. Several features of the family history information, such as the number of family members affected, the degree of relatedness among affected relatives, the occurrence of cancer at younger than usual ages, and the occurrence of cancer in both members of a set of paired organs can lead an alert clinician to consider the possibility that an inherited cancer susceptibility may be present.

Quantitative, cancer site-specific models that incorporate these characteristics of the family history data with the information on environmental and behavioral risk factors are now being developed, and seem likely to result in significant improvements in objective risk assessment. For example, the so-called "Gail Model" for estimating breast cancer risk (which was developed using data from the original BCDDP study, using multivariate logistic regression techniques) incorporates family history of breast cancer (number of first-degree relatives with breast cancer), current age, age at first menses, and age at first

birth to estimate the risk of breast cancer (Gail et al., 1989). This model was successfully used to define participant eligibility for the recently reported Breast Cancer Tamoxifen Prevention Trial (Fisher et al., 1998).

An alternate model, known as "BRCAPRO," uses full pedigree structure data and data on specific transmission patterns, estimates of gene frequency and penetrance, to develop a Bayesian estimate of the probability of carrying a mutation in BRCA1 and BRCA2 (Berry et al., 1997). This model does not include traditional breast cancer risk factors, but it is currently being used in many high-risk breast/ovarian cancer clinics, as part of the genetic counseling process. These quantitative tools represent a more formal and objective means of assessing the information, which can be obtained by interviewing a patient, and then using that information to develop an estimate of cancer risk. Our data suggest that a carefully taken family history, with attention paid to the clinical clues which suggest the presence of an inherited cancer susceptibility, may be able to identify high-risk women in the general population setting. Once identified, these women may be targeted for appropriate surveillance and risk-reduction strategies. Some may be candidates for more formal genetic risk assessment, and consideration of germline mutation testing for the presence of BRCA1/BRCA2 mutations.

However, the family history information must be used with care, since women may be unaware of their family history, or fail to provide the correct information, thereby creating a false negative report. As means to reduce the false negative reports, educating the public regarding the importance of family history information, and the use of standardized and validated family history tools by clinical and public health practitioners

should be considered. An ideal risk assessment model would stratify the population into average, moderate, and high-risk groups with regard to their risk of cancer.

Our studies suggest that family history of breast cancer is an important predictor of ovarian cancer risk. This implies that clinicians who are caring for women with a family history of breast cancer, in particular, in two or more first-degree relatives should monitor their patient's risk of ovarian cancer. In addition, health care providers who are caring for women with ovarian cancer may find it useful to consider carefully the details of breast cancer occurrence among their patients' relatives, as they search for clinically useful clues to the etiology of these cancers.

Primary care physicians, as gatekeepers to the health care system, should be trained to take accurate family histories in order to identify patients who may require a more detailed cancer genetic risk assessment and access to targeted preventive services. Acheson et al. (2000) have reported that family practice physicians discuss family history half of the time during new patient visits, and only 22% of the time during established patient visits. The recognition of a hereditary predisposition to ovarian and breast cancer may have important management implications for both the patient and their relatives. Decisions regarding the use of exogenous hormonal medications, the advisability of risk-reducing surgical options, the frequency and type of cancer surveillance, and the need to consider possible lifestyle modifications in an effort to reduce risk are all affected by the presence of a genetic cancer susceptibility disorder. Through family history information, general practitioners are able to perform an initial genetic risk assessment, and then decide whether to refer or reassure the patient.

Future Directions in Research

Endometrial cancer

We failed to find as association between endometrial cancer risk and a family history of breast cancer. However, because our study included very few younger or premenopausal women, a cohort study of women of all ages could provide additional useful information. This question is not of sufficient scientific importance to warrant mounting such a study specifically to test this hypothesis. Thus, it is likely that further data will only derive from the opportunistic analysis of cohorts established for other reasons. In light of the current trend within cancer epidemiology towards the creation of larger and larger prospective cohort studies designed to address complex issues related to host/environmental interactions in cancer etiology, it is likely that such an opportunity will present itself at some point in the future. If a suitable cohort can be identified, we strongly recommend the use of time-dependent analytic techniques, for the reasons discussed earlier.

Ovarian cancer

Our ovarian cancer analysis detected an association between a family history of breast cancer and the risk of developing ovarian cancer. Furthermore, the results from our detailed family history analyses indicated a pattern consistent with the hereditary breast and ovarian cancer (HBOC) syndrome among some of our cases. One possible way to confirm our results would be to compare the age-specific breast cancer incidence rates in the cohort of family members of the ovarian cancer cases with that of non-cases in a case-control or cohort study of ovarian cancer. This method would require

information on the date of birth, current age, or age at death of unaffected female relatives as well as age at diagnosis of affected relatives. This information was not available in our cohort study.

This methodologic and analytic approach is similar to that used by the Centers for Disease Control to investigate the familial risk of breast cancer in the Cancer and Steroid Hormone Study (CASH) (Claus et al., 1990). A Cox proportional hazard model could be used to analyze time to onset of breast cancer among family members of the ovarian cancer cases and the controls. We could further refine this analysis by taking into account the age of both the proband (ovarian cancer case) and her relatives or in relation to other risk factors of the proband. These analyses would compare the hazard rates and age-specific estimates of cumulative risk of breast cancer to first- and second-degree female relatives of the ovarian cancer cases to the ones from controls. Data from the CASH study could also be used to do similar analyses for ovarian cancer and family history of endometrial cancer.

In the same population-based case-control study, we could also re-evaluate the association between family history of breast cancer and ovarian cancer risk after controlling for carrier status for BRCA1 and BRCA2 genes. The probability of carrying a mutation in BRCA1 or BRCA2 or both could be calculated for each case and control by use of Bayes theorem and Mendelian genetics, assuming an autosomal dominant transmission for both BRCA1 and BRCA2 genes (Berry et al., 1997; Parmigiani et al., 1998). Among predicted carriers and non-carriers, logistic regression could be used to assess the association between case or control status and family history of breast cancer.

In addition, we could calculate the estimates of age-specific ovarian cancer risk by predicted carrier status.

Although the hereditary breast and ovarian cancer syndrome has been associated with the breast cancer susceptibility genes, BRCA1 and BRCA2, a significant proportion (20%) of families, which show a hereditary pattern of susceptibility, i.e., early onset or family history of breast cancer, are in fact BRCA1- or BRCA2-negative (Schubert et al., 1997; Shattuck-Eidens et al., 1997). One possible explanation for this finding is that current testing methods do not detect all BRCA1 or BRCA2 mutations. Alternatively, other unidentified genes may play a significant role in the etiology of breast and ovarian cancers in the BRCA1- BRCA2-negative families. This has important implications for the cancer risk prediction models, which are based on actual BRCA1/BRCA2 mutation testing data (Struewing et al., 1997). In using such models, more research is required in the following areas:

1) Identification of other major rare genes, e.g., "BRCA3", or common susceptibility genes that play a role in ovarian cancer development;
2) Development of more sensitive and specific tests that detect all pathological BRCA1 or BRCA2 mutations;
3) Studies that demonstrate the joint effects of a variety of genes, including common susceptibility genes, which are in the causal pathways in the disease biology, and environmental factors, e.g., oral contraceptive use, in the development of ovarian cancer.

However, before this information becomes available, the family history data can be used as a proxy for shared genetic and environmental factors among family members. At

this stage of our knowledge about the natural history of ovarian cancer, the family history information can be used in risk prediction models without consideration of "why" there is a family history. The population parameter estimates of ovarian cancer risk associated with different patterns of family history, in studies such as ours, could be incorporated in risk prediction models similar to "Gail model". Such models should also include the risk ratios for other risk factors, e.g., age, parity, and hormone replacement therapy use, and baseline age-specific ovarian cancer hazard rate, to assess ovarian cancer risk. The rates from population-based studies with greater number of cases from all age groups could be more informative for age-specific rate calculations. As we learn more about the risk factors for ovarian cancer in new epidemiologic studies, these population-based estimates need to be updated and refined. While any individual risk factor may be predictive of ovarian cancer, comprehensive risk prediction models that include family history information represent the combined influence of all risk factors (genetic, environmental, and behavioral) on the disease phenotype in multiple family members.

REFERENCES

Acheson LS, Wiesner GL, Zyzanski SJ, Goodwin MA, Stange KC. Family history-taking in community family practice: Implications for genetic screening. Genetics in Medicine 2000; 2:180-185.

Anderson DE. Breast cancer in families. Cancer 1977; 40:1855-1860.

Austin H, Drews C, Partridge EE. A case-control study of endometrial cancer in relation to cigarette smoking, serum estrogen levels, and alcohol use. Am J Obstet Gynecol 1993; 169:1086-91.

Berry DA, Parmigiani G, Sanchez J, Schildkraut J, Winer E. Probability of carrying a mutation of breast-ovarian cancer gene BRCA1 based on family history. J Natl Cancer Inst 1997; 89:227-38.

Bewtra C, Watson P, Conway T, Read-Hippee C, Lynch HT. Hereditary ovarian cancer: A clinicopathological study. Int J Gynecol Pathol 1992; 11:180-187.

Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD, Lannom L, Hoover RN. Reproductive, menstrual, and medical risk factors for endometrial cancer: results from a case-control study. Am J Obstet Gynecol 1992; 167:1317-25.

Burke W, Daly M, Garber J, Botkin J, Kahn MJ, Lynch P, McTiernan A, Offit K, Perlman J, Petersen G, Thomson E, Varricchio C. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2. Cancer Genetics Studies Consortium. Health Psychol 1997;16:63-72.

Claus EB, Risch NJ, Thompson WD. Age at onset as an indicator of familial risk of breast cancer. Am J Epidemiol 1990;131:961-72.

Douglas FS, O'Dair LC, Robinson M, Evans DG, Lynch SA. The accuracy of diagnoses as reported in families with cancer: a retrospective study. J Med Genet 1999; 36:309-12.

Eisen A, Rebbeck TR, Wood WC, Weber BL. Prophylactic surgery in women with a hereditary predisposition to breast and ovarian cancer. J Clin Oncol 2000;18:1980-95.

Eerola H, Blomqvist C, Pukkala E, Pyrhonen S, Nevanlinna H. Familial breast cancer in southern Finland: how prevalent are breast cancer families and can we trust the family history reported by patients? Eur J Cancer 2000; 36:1143-8.

Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L, Wolmark N. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998; 90:1371-88.

Fishman A, Dekel E, Chetrit A, Lerner-Geva L, Bar-Am A, Beck D, Beller U, Ben-Baruch G, Piura B, Friedman E, Struewing JP, Modan B. Patients with double primary tumors in the breast and ovary- clinical characteristics and BRCA1-2 mutations status. Gynecol Oncol 2000; 79:74-8.

Frank TS, Manley SA, Olopade OI, Cummings S, Garber JE, Bernhardt B, Antman K, Russo D, Wood ME, Mullineau L, Isaacs C, Peshkin B, Buys S, Venne V, Rowley PT, Loader S, Offit K, Robson M, Hampel H, Brener D, Winer EP, Clark S, Weber B, Strong LC, Thomas A, et al. Sequence analysis of BRCA1 and BRCA2: correlation of mutations with family history and ovarian cancer risk. J Clin Oncol 1998; 16:2417-25.

Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, Mulvihill JJ. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 1989; 81:1879-86.

Go RC, King MC, Bailey-Wilson J, Elston RC, Lynch HT. Genetic epidemiology of breast cancer and associated cancers in high-risk families. I. Segregation analysis. J Natl Cancer Inst 1983; 71:455-61.

Hakala T, Mecklin JP, Forss M, Jarvinen H, Lehtovirta P. Endometrial carcinoma in the cancer family syndrome. Cancer. 1991; 68:1656-9.

Hall JM, Lee MK, Newman B, Morrow JE, Anderson LA, Huey B, King MC. Linkage of early-onset familial breast cancer to chromosome 17q21. Science. 1990;250:1684-9.

Hoover R, Fraumeni JF, Everson R, Myers MH. Cancer of the uterine corpus after hormonal treatment for breast cancer. Lancet 1976; 1:885-7.

Hopper JL, Carlin JB. Familial aggregation of a disease consequent upon correlation between relatives in a risk factor measured on a continuous scale. Am J Epidemiol 1992; 136:1138-47.

Kelsey JL, LiVolsi VA, Holford TR, Fischer DB, Mostow ED, Schwartz PE, O'Connor T, White C. A case-control study of cancer of the endometrium. Am J Epidemiol 1982; 116:333-342.

Kerber RA, Slattery ML. Comparison of self-reported and database-linked family history of cancer data in a case-control study. Am J Epidemiol 1997; 146:244-8.

Khoury MJ, Beaty TH, Liang KY. Can familial aggregation of disease be explained by familial aggregation of environmental risk factors? Am J Epidemiol 1988; 127:674-83.

Knudson AG. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA 1971; 68:820-823.

Kvale G, Heuch I, Nilssen S. Reproductive factors and cancers of the breast and genital organs--are the different cancer sites similarly affected? Cancer Detect Prev 1991; 15:369-77.

La Vecchia C, Franceschi S, Decarli A, Gallus G, Tognoni G. Risk factors for endometrial cancer at different ages. J Natl Cancer Inst 1984; 73:667-71.

Love RR, Evans AM, Josten DM. The accuracy of patient reports of a family history of cancer. J Chronic Dis 1985; 38:289-93.

Lynch HT, Krush AJ, Lemon HM, Kaplan AR, Condit PT, Bottomley RH. Tumor variation in families with breast cancer. JAMA 1972; 222:1631-1635.

Lynch HT, Harris RE, Guirgis HA, Maloney K, Carmody LL, Lynch JF. Familial association of breast/ovarian carcinoma. Cancer 1978; 41:1543-1549.

Lynch HT, Watson P, Tinley S, Snyder C, Durham C, Lynch J, Kirnarsky Y, Serova O, Lenoir G, Lerman C, Narod SA. An update on DNA-based BRCA1/BRCA2 genetic counseling in hereditary breast cancer. Cancer Genet Cytogenet 1999;109:91-8.

Mackey SE, Creasman WT. Ovarian cancer screening. J Clin Oncol 1995; 13:783-793.

MacMahon B. Risk factors for endometrial cancer. Gynecol Oncol 1974; 2:122-9.

Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science. 1994;266:66-71.

Nelson CL, Sellers TA, Rich SS, Potter JD, McGovern PG, Kasha LH. Familial clustering of colon, breast, uterine, and ovarian cancers as assessed by family history. Genet Epidemiol 1993; 10:235-244.

Olson JE, Sellers TA, Anderson KE, Folsom AR. Does a family history of cancer increase the risk for postmenopausal endometrial carcinoma? A prospective cohort study and a nested case-control family study of older women. Cancer 1999; 85:2444-2449.
Parent ME, Ghadirian P, Lacroix A, Perret C. The reliability of recollections of family history: implications for the medical provider. J Cancer Educ 1997; 12:114-20.

Parmigiani G, Berry D, Aguilar O. Determining carrier probabilities for breast cancer-susceptibility genes BRCA1 and BRCA2. Am J Hum Genet 1998; 62:145-58.

Piver MS, Mettlin CJ, Tsukada Y, Nasca P, Greenwald P, McPhee ME. Familial ovarian cancer registry. Obstet Gynecol 1984; 64:195-199.

Robson M, Gilewski T, Haas B, Levin D, Borgen P, Rajan P et al. BRCA-associated breast cancer in young women. J Clin Oncol 1998; 16:1642-9.

Risinger JI, Barrett JC, Watson P, Lynch HT, Boyd J. Molecular genetic evidence of the occurrence of breast cancer as an integral tumor in patients with the hereditary nonpolyposis colorectal carcinoma syndrome. Cancer 1996; 77:1836-1843.

Schildkraut JM, Risch N, Thompson WD. Evaluating genetic association among ovarian, breast, and endometrial cancer: Evidence for a breast/ovarian cancer relationship. Am J Hum Genet 1989; 45:521-9.

Schubert EL, Lee MK, Mefford HC, Argonza RH, Morrow JE, Hull J, Dann JL, King MC. BRCA2 in American families with four or more cases of breast or ovarian cancer: recurrent and novel mutations, variable expression, penetrance, and the possibility of families whose cancer is not attributable to BRCA1 or BRCA2. Am J Hum Genet 1997; 60:1031-40.

Shattuck-Eidens D, Oliphant A, McClure M, McBride C, Gupte J, Rubano T, Pruss D, Tavtigian SV, Teng DH, Adey N, Staebell M, Gumpper K, Lundstrom R, Hulick M,

Kelly M, Holmen J, Lingenfelter B, Manley S, Fujimura F, Luce M, Ward B, Cannon-Albright L, Steele L, Offit K, Thomas A, et al. BRCA1 sequence analysis in women at high risk for susceptibility mutations. Risk factor analysis and implications for genetic testing. JAMA 1997; 278:1242-50.

Scott RJ, McPhillips M, Meldrum CJ, Fitzgerald PE, Adams K, Spigelman AD, du Sart D, Tucker K, Kirk J. Hereditary nonpolyposis colorectal cancer in 95 families: differences and similarities between mutation-positive and mutation-negative kindreds. Am J Hum Genet 2001; 68:118-127.

Shih HA, Nathanson KL, Seal S, Collins N, Stratton MR, Rebbeck TR, Weber BL. BRCA1 and BRCA2 mutations in breast cancer families with multiple primary cancers. Clin Cancer Res 2000; 6:4259-64.

Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, Timmerman MM, Brody LC, Tucker MA. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 1997; 336:1401-8.

Theis B, Boyd N, Lockwood G, Tritchler D. Accuracy of family cancer history in breast cancer patients. Eur J Cancer Prev 1994; 3:321-7.

Verhoog LC, Brekelmans CT, Seynaeve C, van den Bosch LM, Dahmen G, van Geel AN et al. Survival and tumour characteristics of breast-cancer patients with germline mutations of BRCA1. Lancet 1998; 351:316-21.

Watson P, Lynch HT. Extracolonic cancer in hereditary nonpolyposis colorectal cancer. Cancer 1993; 71:677-85.

Weiderpass E, Persson I, Adami HO, Magnusson C, Lindgren A, Baron JA. Body size in different periods of life, diabetes mellitus, hypertension, and risk of postmenopausal endometrial cancer (Sweden). Cancer Causes Control 2000; 11:185-92.

Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, Collins N, Gregory S, Gumbs C, Micklem G. Identification of the breast cancer susceptibility gene BRCA2. Nature. 1995;378:789-92.

APPENDIX A

RESEARCH DESIGN AND METHODS

General Design

The purpose of our studies were to examine further the possible role of family history of breast cancer as a risk factor for endometrial and ovarian cancer, using the prospective cancer incidence data collected in the Breast Cancer Detection Demonstration Project (BCDDP) (Schairer et al. 2000) Follow-up Cohort Study. This study was begun by the National Cancer Institute in 1979 and continued to 1998.

The Follow-up Study was conducted in four phases. The first phase, carried out between 1979 and 1986, involved the administration of a baseline and up to six annual telephone interviews by the personnel at the BCDDP screening centers. Between 1987 and 1998, phase II (1987-1989), III (1993-1995), and IV (1995-1998) were conducted through self-administered mailed questionnaires to all participants not known to be dead. In addition, attempts were made to conduct follow-up interviews by telephone for all non-respondents to the mailed questionnaires.

All eligible BCDDP participants who were interviewed at baseline (1979-1980) are included in this cohort analysis. Participants with a family history of breast cancer (i.e., the "exposure" of interest) will be compared with those without a family history of breast cancer with regard to their risk of developing endometrial or ovarian cancer.

Study Population

The population for the Follow-up Cohort Study consists of a subset of the participants in the BCDDP, a breast cancer screening program that was designed to demonstrate to the medical profession and the public the benefits of screening in the early detection of breast cancer. This project provided up to five annual breast examinations to

283,222 women at 29 screening centers in 27 cities throughout the United States. More than 99 percent of the participants were between the ages of 35 and 74 with a median age of 50 years. The majority of the participants were white (88.3%), with small percentages of blacks (5.3%) and Asians (3.0%).

The Follow-up Study was initiated by the National Cancer Institute in 1979. Women who had participated in the BCDDP, both those who completed all five annual screening visits as well as those who did not, were considered eligible for inclusion. The Follow-up Study included the following four groups, on the basis of their status at their last screening visit: 1) all screening participants who received a recommendation for surgical consultation but did not have either a biopsy or aspiration performed (n=9,628); 2) all subjects who had breast surgery performed during the screening program, with no evidence of malignant disease (n=25,114); 3) all subjects who were diagnosed with breast cancer (n= 4,275); and 4) a sample of women who were not recommended for surgical consultation and did not undergo a biopsy (n= 25,165). The total number of subjects in the cohort selected for follow-up was 64,182. The Special Studies Institutional Review Board at the National Cancer Institute approved the Follow-up Study, and appropriate informed consent was obtained from participants.

Methods and Materials

The Follow-up Study was conducted in 4 phases. The first phase was carried out between 1979 and 1986. During this phase a baseline telephone interview (Form B) was administered by personnel at the BCDDP screening centers at the fifth year screening visit for those still enrolled in the screening project, or during the first year of the

Follow-up Study. Subsequently, up to six annual telephone interviews (Form A) were administered each year to those who had completed a baseline interview. The participants were mailed a letter a few weeks before each interview explaining the purpose of the Follow-up Study, the voluntary nature of participation in the study, and indicating that the participants would be contacted in the near future to answer questions on the enclosed forms.

Between 1987 and 1998, phase II (87-89), III (93-95), and IV (95-98) interviews were conducted through self-administered mailed questionnaires to all participants not known to be dead. A letter describing the purpose of the study at each phase along with a medical records release form was included with the questionnaires. Three weeks after a questionnaire was sent out, reminder postcards were sent to non-respondents. Three weeks later, a second questionnaire was sent to those who didn't respond to the reminders. In addition, attempts were made to conduct follow-up interviews by telephone for all non-respondents to the mailed questionnaires. Numerous efforts were made to locate study participants and to obtain vital status. If respondents could not be traced by contacting neighbors or family members, other tracing mechanisms such as motor vehicle offices, the National Death Index, selected population-based tumor registries, the Health Care Financing Administration, and credit bureaus were used. For all participants known to be deceased, death certificates were obtained through phase III; for phase IV, we used cause of death coding by the National Death Index (NDI).

The cohort was also linked to 12 state cancer registries with the last known address of each participant used as her state of residence. In the ovarian cancer follow-up study, 71% (n=35,412) of those who answered the baseline interview (n=49,975) and 73%

(n=30,882) of those who answered the phase II interview (n=30,882) were linked to state cancer registries. In the endometrial cancer follow-up study, 71% (n=26,780) of those who answered the baseline interview (n=37,583) and 74% (n=23,324) of those who answered the phase II interview (n=31,569) were linked to state cancer registries.

Data on race, education, income, height and weight were available from screening visits between 1973-1979. The information collected at the baseline interview (Form B - phase I) included the following:

- age at menarche;
- number of live births;
- age at first live birth;
- ever use of oral contraceptives (if yes: number of years taken and age at first use);
- age at menopause;
- ever use of female hormones other than birth control pills (if yes: reasons for use, number of years taken, and age at first use);
- family history of breast cancer in specific blood relatives (mother, sister, daughter, grandmother, aunt) including the number in each category affected with breast cancer;
- menopausal status (including date and reason for periods stopping) (menopause was defined as no period having occurred within the three months prior to interview);
- removal of the uterus and/or ovaries (if yes: year of surgery); and
- breast biopsy resulting in either benign or malignant diagnoses.

Information on all these factors, except for the first four variables was also collected in phases II-IV.

The following information that was not collected during phase I of the study, was collected during phases II, and III:

- a more detailed family history of breast cancer, including an enumeration of all first and second-degree relatives (including half-sisters and both maternal and paternal lineage grandmothers and aunts), the relative's age at breast cancer diagnosis and information regarding whether the breast cancer was unilateral or bilateral;
- ever use of estrogen and progestin pills in the same month (if yes: age at first use, total duration of use, and number of days in the month progestin pills were taken);
- medical history, including diabetes, osteoporosis, bone fractures, new cancers (including date of diagnosis);
- date of first diagnosis of ovarian cancer or endometrial cancer;
- tobacco and alcohol use;
- usual dietary habits and use of vitamins;
- activity level;
- physical parameters, including both “usual” and current adult height, weight and body shape.

Information on all these factors, except for the last four variables was also collected in phase IV. Finally, data regarding recent blood pressure, cholesterol, and age at last childbirth were available from phase III.

Endometrial and ovarian cancer cases were identified through self-report on the follow-up questionnaires (phases II, III, and IV), pathology reports, death certificates, and State Cancer Registries. Medical records and pathology reports were sought for participants who reported a cancer diagnosis and who had completed the medical release form during the follow-up period. Nosologists reviewed the pathology reports and then coded the cancer diagnoses onto a pathology form according to standard ICD_O (179.0, 179.9, 182.0) and ICD_9 (179X, 179.9, 182.0, 183.8, 183.9, 233.2) codes for endometrial cancer and ICD_O (183.0, 183.3, 183.4, 183.5, 183.8, 183.9) and ICD_9 (183.0, 183.3, 183.4, 183.5, 183.8, 183.9, 236.2) codes for ovarian cancer. For the endometrial or ovarian cancer cases identified by death certificate, the date of diagnosis was determined by death certificate if 'time since onset of the disease caused death' was specified or by date of diagnosis from State Cancer Registries. Otherwise, other sources such as medical information from earlier interviews or date of bilateral oophorectomy/hysterectomy if the individual had this procedure done were used.

Data Management

Data management for phase I interviews was handled by the Data Management and Analysis Center (DMAC) in Philadelphia and for phases II through IV was coordinated by WESTAT, INC. at the direction of the National Cancer Institute. An automated management system was designed by WESTAT that incorporated the management of the mailings and receipt of the questionnaires, the tracing of the subjects, telephone interview follow-up, and the mailings for and receipt of the death certificates. An additional system was used for the mail-out and receipt of medical records. Quality control procedures

were observed throughout the entire Follow-up Study by using uniform and project-wide data collection forms, and trained interviewers and coders. A COBOL edit program was devised to check all data for errors made in coding or keying the data, such as range or skip pattern errors. In addition, WESTAT coordinated the retrieval of pathology reports and matching of the State Cancer Registry data to the study participants.

Analytic Data Set

Endometrial cancer study response rates: Of the 64,182 subjects selected for participation in the Follow-up Study, 61,431 (95.7 percent) completed a baseline interview (Table 1). Of those who had completed a baseline interview (phase I), 37, 583 (62%) were eligible for the endometrial cancer study. Women who had a hysterectomy (n=23,211) or endometrial cancer (n=637) before the baseline interview were excluded from this study. Of 37, 583 eligible women, 31,568 (84%) completed the phase II interview, 27,526 (73%) completed the phase III and 26,225 (70%) completed the phase IV interview.

Ovarian cancer study response rates: Of the 61,431 participants who completed a baseline interview (Table 2), 49,975 (81%) were eligible for the ovarian cancer study. Women with bilateral oophorectomy (n=11,358), ovarian cancer (n=93), or death (n=5) before the baseline interview were excluded from the study. Of 49,975 eligible women, 42,069 (84%) completed the phase II interview, 36,624 (73%) completed the phase III and 34,826 (70%) completed the phase IV interviews.

Case definitions: Due to methodologic advantages of different case definitions, I considered four options for each study (Tables 3-6). Because 85 per cent of self-reported

endometrial cancers for which pathology reports were available were confirmed as cancers, in case definitions 1 and 2, the self-reported cancers for which pathology reports were *not* available are included as cases. Also, in the ovarian cancer study, because 72 per cent of self-reported ovarian cancers for which pathology reports were available were confirmed as cancers, in case definitions 1 and 2, the self-reported cancers for which pathology reports were not available are included as cases. According to a correction formula for bias from the misclassification of disease status among non-confirmed cases (Brenner and Gefeller 1993), the corrected estimate of relative risk is not expected to be different from the uncorrected estimate. This is due to the fact that the outcome misclassification (i.e., ovarian/endometrial cancer) among the non-confirmed cases is non-differential, i.e., independent of exposure status.

In case definition 1, cases were only identified before their last questionnaire date, whereas in case definition 2, cases were also identified after their last questionnaire date, through death certificates and state cancer registries. Case definitions 3 and 4 are identical to case definitions 1 and 2, except that the self-reported cases that were not confirmed by pathology report or linkage to the State Cancer Registries are excluded.

Participants who completed a baseline interview with a prior endometrial cancer or hysterectomy or a prior ovarian cancer or bilateral oophorectomy were excluded from analysis in the endometrial and ovarian cancer studies, respectively. The entry date for the participants was the date of completion of the baseline questionnaire (FORM B). The exit date was one of the following based on the case definition: 1) case definitions 2 and 4 - the earliest of the following dates: a) hysterectomy in endometrial cancer study or bilateral oophorectomy in ovarian cancer study, b) endometrial or ovarian cancer

diagnosis, c) study end date, which is the date of completion of phase IV questionnaire or for non-respondents to phase IV, the date that they would have completed phase IV if still alive, and d) date of death or State Cancer Registry diagnosis date if this date is $\leq$ study end date; 2) case definitions 1 and 3 – the earliest of the following dates: a) hysterectomy in endometrial cancer study or bilateral oophorectomy in ovarian cancer study, b) endometrial or ovarian cancer diagnosis, c) last questionnaire date. In the endometrial cancer Follow-up Study, considering exit dates one and two, 518,747 and 454,681 person-years were accumulated for 37,583 subjects included in the analysis after the exclusion of endometrial cancer and hysterectomy cases that occurred prior to baseline interview. The corresponding person-years in the ovarian cancer study were 715,914 and 628,387 for 49,975 subjects included in the analysis after the exclusion of ovarian cancer and bilateral oophorectomy cases that occurred prior to baseline interview.

With regard to the main exposure, women who reported breast cancer in a sister, mother, and/or daughter are classified as having a 1st degree family history and those who reported a family history in grandmother, and/or aunt classified as 2nd degree family history. We examined the following covariates in the analyses: age at menopause (all phases), age at menarche (baseline), menopausal status (all phases), attained age (all phases), body mass index (BMI: screening visits, II, III), hormone replacement therapy (HRT) and duration of use (all phases), oral contraceptive (OC) use (baseline), smoking (phase II and III), parity (baseline), diabetes (phases II-IV), and personal history of breast cancer (all phases).

Sample Size and Power

Table 7 indicates the estimated statistical power of the endometrial cancer Follow-up Study. This estimation considers exposure (breast cancer family history) prevalences of 22%, 28%, and 46% (derived from the BCDDP population after the exclusion of participants with unsure exposure status) corresponding to 1st degree, 2nd degree, and 1st or 2nd degree family history of breast cancer. The power calculations were calculated for relative risks (RR) ranging from 1.2 to 1.5 with alpha equal to 0.05 (two sided) for study sizes of 503,408; 368,594; and 402,673 person-years after the exclusion of women with unknown breast cancer family history in each category of the exposure, and a rate of 130 endometrial cancers per 100,000 person-years in the unexposed cohort. For each exposure prevalence, power will be greater than 80% to detect a relative risk of 1.3.

Table 8 indicates the estimated statistical power of the ovarian cancer study. This estimation considers exposure (breast cancer family history) rates of 22%, 28%, and 46% (derived from the BCDDP population after the exclusion of participants with unsure exposure status) corresponding to 1st degree history of breast cancer, 2nd degree history of breast cancer, and 1st or 2nd degree history of breast cancer. The power calculations take into account relative risks (RR) ranging from 1.2 to 1.5 with alpha equal to 0.05 (two sided) for study sizes of 694,105; 506,929; and 554,867 person-years after the exclusion of women with unknown breast cancer family history in each category; and rate of 52 ovarian cancers per 100,000 person-years in the unexposed cohort. For each exposure prevalence rate, power will be about 80% or higher to detect a relative risk of 1.4.

Data Analyses

Choice of statistical model: The primary objectives of these analyses are to determine whether incidence rates of endometrial or ovarian cancer are higher in women with a family history of breast cancer than in women with no family history. The statistical analysis was done by using Poisson regression (Breslow and Day, 1987), a model that is useful for studying rare diseases in a large cohort.

An essential feature of the analysis of cohort data is accounting for the time at risk of disease that is contributed by individuals while they are under observation. This feature allows counting for incomplete follow-up of some of the study participants. Poisson regression is often applied in epidemiologic studies when employing a person-time approach, which allows calculation of rates. This statistical model allows for variability in follow-up times. Follow-up time is incorporated into Poisson regression in the following way: subjects contribute person-years at risk only as long as they are under observation, and the person-years at risk are allocated to exposure categories in a time-dependent manner.

While logistic regression is often used in the analysis of case-control and fixed (as opposed to dynamic) cohort studies, it does not account for variability in follow-up times and changes in covariate values over time. In logistic regression, the implicit assumption is that each subject is followed for the same amount of time, or that differences in follow-up time have no effect on the study findings. In a study by Callas et al. (1998), comparing proportional hazards, Poisson, and logistic regression modeling of occupational cohort data, the logistic model provided less precise estimates than the other two. In this follow-up cohort study, because of the lost-to-follow-up due to refusal to fill

out the questionnaire, inability to locate the study participants, and death, logistic regression is not the analysis of choice.

On the other hand, a Cox proportional hazards model that accounts for changes over time in study participants at risk and in covariates could also be a model of choice in the analysis of our data. This model is used for the analysis of *continuous* survival time data and its underlying assumption is that at *any given time*, the hazard in those with a certain characteristic (exposed) is a multiple of some underlying hazard, e.g., the hazard in the unexposed. However, this model analyzes each individual's data versus a grouped data and is computationally very intensive. We chose to use a Poisson regression model, which analyzes grouped data and yields the same results as a Cox proportional hazards model, in our study.

Poisson regression makes the assumption of exponential baseline survival time (dependent variable Y is a count that follows the Poisson distribution) and therefore it specifies that the magnitude of the rate (outcome variable) is an exponential function of a linear combination of covariates and unknown parameters:

$$\text{Events/person-time} = \text{Rate} = \exp(B_o + B_1X_1 + B_2X_2 + \ldots + B_kX_k)$$

$$\log(\text{rate}) = B_o + B_1X_1 + B_2X_2 + \ldots + B_kX_k$$

This model is implemented by stratifying counts of events (endometrial or ovarian cancer) and person-years of observation into a multi-dimensional table of exposure levels and covariates, and examining the incidence rates in the cells of the table. By finer stratification of the variables, giving smaller cells, the approximation of the parameter estimates can be improved (Kelsey et al., 1996). An additional assumption underlying

the use of this model is that disease rates are constant within each of the cells that make up the cross-classification of exposures and confounding variables.

Time-dependent variables considered in the analyses: In these analyses, time-dependent variables include attained age, diabetes, smoking, BMI, hypertension, personal history of breast cancer, menopausal status, female hormone use, and family history of breast cancer. Family history variables were defined to indicate the age of the participant at the mid-point between first report of exposure and the prior interview. Other time-dependent variables were defined based on the age that the participant reported that exposure or was diagnosed with that exposure.

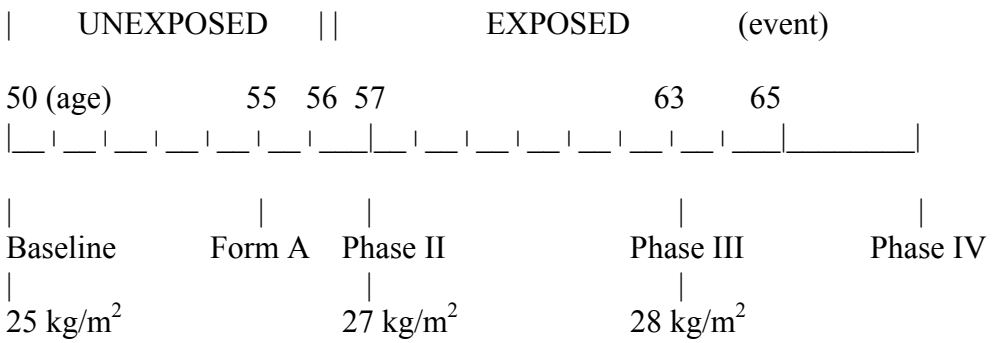
For example, if a subject reported a female family member with breast cancer on the phase II interview, the time-dependent family history variable would be set to the age of the participant at the mid-point between phase II interview and the prior Form A interview. Participants with no reported family history would be coded 999 for this variable.

In addition, time-dependent variables were created to indicate a 2nd relative of that type with breast cancer. If a subject reported one sister with breast cancer on baseline interview (lifetime family history) and another sister with breast cancer on the final Form A and the phase II interview (lifetime family history) indicated 2 sisters with breast cancer, then the "at least 2 sisters with breast cancer" variable would be set to the age at the mid-point between the final Form A and the prior Form A reports and to 999 otherwise, whereas the other time-dependent variable would be set to the age of the baseline report.

Another example of a time-dependent variable such as diabetes is illustrated here by the manner in which participants were classified. The diabetes variable was created based on the month and year of the first diagnosis reported in phases II-IV. A time-dependent variable of diabetes considers the age of individual at first diagnosis of diabetes. In addition, another time-dependent variable indicates the age at first time they are 'unknown if diabetes.' For the first variable, the age at first diagnosis was coded if they had diabetes and 999 was coded if never had diabetes. For the unknown variable, age at first time they were 'unknown if diabetes' was coded and 999 was coded if never had diabetes or had diabetes. The same method was used to create all the other time-dependent variables.

Person-year allocations in the statistical models: Person-years were allocated into the cells of attained age at each year throughout the follow-up period (i.e., 0-49, 50-54, 55-59,60-64, 65-69, 70-74, >74). Person-years were also classified according to whether the participants in the Follow-up Studies had a family history of breast cancer (exposure of interest) or were exposed to other factors. Throughout the Follow-up Study, a participant could contribute person-years to more than one cell. The following example illustrates how the person-years would be allocated for women who entered the study at the age of 50, reported a first-degree female family member with breast cancer on the phase II interview at the age of 57 (i.e., they are 56 years old at the mid-point between the last Form A and phase II interviews), and exited the study (e.g., diagnosed with endometrial or ovarian cancer) at the age of 65. All person-years prior to the age of 56 were included in the unexposed categories of the 50-54 and 55-59 attained age cells and all person-years after the age of 56 (including 56) were included in the exposed

categories of the 55-59, 60-64, and 65-69 attained age cells. In addition, the number of events (e.g., endometrial or ovarian cancer) was allocated to this latter cell.



Now, let's assume that we are also interested in including another time-dependent variable such as BMI and a non-time-dependent variable such as race in the model. The BMI time-dependent variable was created based on the following categories: <22.05, 22.06-25.07, 25.08-27.85, 27.86-32.06, >32.06, and unknown. The race variable was categorized as white, Hispanic, black, and other, and the first-degree family history variable included no first-degree family history, first-degree family history, and unknown first-degree family history categories. Different categories of each variable are indicated by numerical numbers, e.g., BMI less than 22.05 was denoted by 1, and the unknown category by 6. For ten women with the characteristics shown in the diagram above, who were also white with a BMI of 25 kg/m^2 at the baseline (age of 50), BMI of 27 kg/m^2 on phase II (age of 57), and BMI of 28 kg/m^2 on phase III (age of 63), the following cross-classifications for person-year and event calculations are indicated.

As shown in Table 9, for these ten women, 60 person-years were allocated to the unexposed category (no first-degree family history) and 90 person-years to the exposed category (first-degree family history). In each of these exposure groups, person-years were also allocated to different attained age and BMI categories.

The unadjusted rate ratio of the association between endometrial or ovarian cancer risk and first-degree family history can be calculated by division of the rate among exposed by the rate among unexposed. In this example, women who exited the study due to endometrial or ovarian cancer diagnosis also had a first-degree family history of breast cancer. In the BCDDP dataset, there were cases of endometrial or ovarian cancer among the unexposed group as well, so the number of events in this group was not zero.

References

Brenner H and Gefeller O. Use of the positive predictive value to correct for disease misclassification in epidemiologic studies. Am J Epidemiol 1993; 138:1007-1015.

Breslow NE, Day NE. Statistical Methods in Cancer Research: Vol II. The Design and Analysis of Cohort Studies. Lyon: International Agency for Research on Cancer, IARC Scientific Publications 1987; No. 82:131-35,160-67,185.

Callas PW, Pastides H, Hosmer DW. Empirical comparisons of proportional hazards, Poisson, and logistic regression modeling of occupational cohort data. Am J Ind Med 1998; 33: 33-47.

Kelsey JL, Whittemore AS, Evans AS, Thompson WD. Methods in observational epidemiology. New York: Oxford University Press 1996; 138-62.

Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Estrogen-progestin replacement and risk of breast cancer. JAMA 2000; 284:691-4.

Table 1. Cohort selection in the BCDDP endometrial cancer Follow-up Study

Recruitment (1973-75) 283,222 Screenees

Selected for Follow-up ÷	Cancers	Benigns	Recommended	Normals	Total
	4,275	25,114	9,628	25,165 =	64,182
	∴	∴	∴	∴	∴
Answered ÷ baseline interview (1979-85)	3,729	24,403	9,103	24,196 =	61,431
Eligible for ÷ EC study	2,333	14,289	5,825	15,136 =	37,583

Table 2. Cohort selection in the BCDDP ovarian cancer Follow-up Study

Recruitment (1973-75) 283,222 Screenees

Selected for Follow-up ÷	Cancers	Benigns	Recommended	Normals	Total
	4,275	25,114	9,628	25,165 =	64,182
	∴	∴	∴	∴	∴
Answered ÷ baseline interview (1979-85)	3,729	24,403	9,103	24,196 =	61,431
Eligible for ÷ OC study	3,010	19,750	7,531	19,684 =	49,975

Table 3. Definition of cases and their exit dates in endometrial cancer Follow-up Study

Case definitions	Exit dates
Case 1: any self report (excluding those contradicted by pathology), path report, or either state cancer registry report before last questionnaire date.	*Exit 1* - The earliest of the following dates: a) hysterectomy, b) endometrial cancer diagnosis (dx), c) last questionnaire date.
Case 2: any self report (excluding those contradicted by pathology), path report, or either cancer registry report before last questionnaire date, or death before end date.	*Exit 2* - The earliest of the by following dates: a) hysterectomy, b) endometrial cancer dx, c) study end date, d) date of death or state cancer registry dx date if this date is $\leq$ study end date.
Case 3: confirmed self report (excluding those contradicted by pathology), path report, or state cancer registry report before last questionnaire date.	*Exit 3* - Same as Exit 1.
Case 4: confirmed self report (excluding those contradicted by pathology), path report, or either cancer registry report before last questionnaire date, or death before end date.	*Exit 4* - Same as Exit 2.

Table 4. Number of cases by different identification sources and case definitions in the BCDDP endometrial cancer Follow-up Study

Sources of Cases	Case Definitions			
	Case 1	**Case 2**	**Case 3**	**Case 4**
Self report (no pathology & no state registry)	47	47	0	0
Self-report & pathology	404	404	404	404
Pathology report only	39	39	39	39
Death certificate, no state registry*	0	31	0	31
Self report & state registry	16	16	16	16
Death certificate & state	0	16	0	16
State registry only	36	95	36	95
Total	542	648	495	601

*one self-reported case was included.

Table 5. Definition of cases and their exit dates in the ovarian cancer Follow-up Study

Case definitions	Exit dates
Case 1: any self report (excluding those contradicted pathology), path report, or state cancer registry report before last questionnaire date.	*Exit 1* - The earliest of the following dates : a) bilateral oophorectomy, b) ovarian cancer diagnosis (dx), c) last questionnaire date
Case 2: any self report (excluding those contradicted by pathology), path report, or either cancer registry report before last questionnaire date, or death before end date.	*Exit 2* - The earliest of the following dates: a) bilateral oophorectomy, b) ovarian cancer diagnosis, c) study end date, d) date of death or state cancer registry dx date if this date is $\leq$ study end date.
Case 3: confirmed self report (excluding those contradicted by pathology), path report, or state cancer registry report before last questionnaire date.	*Exit 3* - Same as Exit 1.
Case 4: confirmed self report (excluding those contradicted by pathology), path report, or either cancer registry report before last questionnaire date, or death before end date.	*Exit 4* - Same as Exit 2.

Table 6. Number of cases by different identification sources and case definitions in the BCDDP ovarian cancer Follow-up Study

Sources of Cases	Case 1	Case 2	Case 3	Case 4
Self report (no pathology & no state registry)	20	20	0	0
Self-report & pathology	140	141	140	141
Pathology report only	5	5	5	5
Death certificate, no state registry*	0	107	0	107
Self report & state registry	4	4	4	4
Death certificate & state$^{\varphi}$	7	46	7	46
State registry only	21	39	21	39
Total	197	362	177	342

* 2 self-reported cases were included; $^{\varphi}$ 6 self-reported cases were included.

Table 7. Power calculation in the BCDDP endometrial cancer Follow-up Study

Prevalence of breast cancer family history (%)	Rate Ratio	Endometrial cancer rate (per 100,000) among unexposed [φ]	Person-years*	Power (%)
22 (1st degree relative)	1.2	130	503,408	54
	1.4	130	503,408	97
	1.5	130	503,408	100
28 (2nd degree relative)	1.2	130	368,594	48
	1.3	130	368,594	80
	1.4	130	368,594	95
	1.5	130	368,594	99
46 (1st and or 2nd degree)	1.2	130	402,673	59
	1.3	130	402,673	89
	1.4	130	402,673	99
	1.5	130	402,673	100

alpha = 0.05 (two-sided); [φ] unexposed = participants without a 1st or 2nd degree family history of BC;
* After the exclusion of women with unsure BC family history information.

Table 8. Power calculation in the BCDDP ovarian cancer Follow-up Study

Prevalence of breast cancer family history (%)	Rate ratio	Ovarian cancer rate (per 100,000) among unexposed φ	Person-years*	Power (%)
22 (1st degree relative)	1.2	52	694,105	34
	1.4	52	694,105	83
	1.5	52	694,105	95
28 (2nd degree relative)	1.2	52	506,929	30
	1.3	52	506,929	55
	1.4	52	506,929	78
	1.5	52	506,929	91
46 (1st or 2nd degree)	1.2	52	554,867	37
	1.3	52	554,867	66
	1.4	52	554,867	88
	1.5	52	554,867	97

alpha = 0.05 (two-sided); φ unexposed = participants without a 1st or 2nd degree family history of BC;
* After the exclusion of women with unsure BC family history information.

Table 9. An example of the person-year tabulation in the calculation of rate ratios in Poisson regression models used in the BCDDP follow-up studies

Attained age	BMI	Race	Person-years	Number of events
Never 1st degree Family History				
0-49	---	---	---	---
>49-54	2	1	10 x 4 years	0
>54-59	2	1	10 x 2 year	0
>59-64	---	---	---	---
>64-69	---	---	---	---
>69-74	---	---	---	---
>74-120	---	---	---	---
Total			10 x 6 years	0
Ever 1st degree Family History				
0-49	---	---	---	---
>49-54	---	---	---	---
>54-59	2	1	10 x 1 year	0
	3	1	10 x 2 years	0
>59-64	3	1	10 x 4 years	0
	4	1	10 x 1 year	0
>64-69	4	1	10 x 1 year	10
>69-74	---	---	---	---
>74-120	---	---	---	---
Total			10 x 9 years	10

APPENDIX B

ADDITIONAL TABLES

Table 1. Rate ratios (RR) of endometrial cancer associated with selected factors in BCDDP endometrial cancer Follow-up Study, 1979-1998

Risk factor	No. of Person-Years	No. of Cases (n=648)	RR* (95% CI)
Attained age (yrs)			
<50	47,881	15	1.0 (reference)
50-54	72,040	50	1.4 (0.8-2.7)
55-59	100,680	102	1.5 (0.8-2.9)
60-64	101,318	144	1.8 (0.9-3.4)
65-69	82,058	144	2.0 (1.0-3.8)
70-74	55,842	99	1.9 (1.0-3.7)
75+	58,927	94	1.8 (0.9-3.4)
Education			
<High school	61,610	68	1.0 (reference)
High school	209,637	253	1.1 (0.9-1.5)
Some college	121,173	167	1.2 (0.9-1.7)
College graduate +	122,025	155	1.2 (0.9-1.6)
Unknown	4,302	5	1.1 (0.4-2.7)
Race			
White	451,128	588	1.0 (reference)
Hispanic	11,692	13	1.0 (0.6-1.7)
Black	19,998	8	0.3 (0.2-0.7)
Other	35,930	39	1.0 (0.7-1.3)
Body mass index (kg/m^2)			
<22.05	185,058	174	1.0 (reference)
22.06-25.07	154,982	195	1.4 (1.1-1.7)
25.08-27.85	80,203	106	1.5 (1.1-1.9)
27.86-32.06	53,369	80	1.7 (1.3-2.2)
32.07+	26,508	67	3.3 (2.5-4.4)
Unknown	18,625	26	1.5 (1.0-2.3)
Parity			
0	79,425	139	1.0 (reference)
1	63,325	82	0.8 (0.6-1.0)
2	151,881	203	0.8 (0.7-1.0)
≥3	224,116	224	0.6 (0.5-0.8)
Oral contraceptive use			
Never	364,369	515	1.0 (reference)
Ever	153,724	132	0.7 (0.6-0.9)
Unknown	654	1	0.9 (0.1-6.1)

Table 1. Rate ratios (RR) of endometrial cancer associated with selected factors in BCDDP endometrial cancer Follow-up Study, 1979-1998

Risk factor	No. of Person-Years	No. of Cases (n=648)	RR* (95% CI)
Duration of oral contraceptive use			
No use	364,967	516	1.0 (reference)
<3	73,976	81	0.9 (0.7-1.1)
3-<9	50,216	31	0.6 (0.4-0.8)
≥9	25,776	13	0.4 (0.3-0.8)
Unknown	3,182	7	1.5 (0.7-3.2)
Estrogen/estrogen-progestin (ERT-PRT) use			
No use	303,995	254	1.0 (reference)
Estrogen only	91,118	205	Ψ 2.4 (2.0-2.8)
Estrogen-progestin/ PRT (estrogen unknown)	82,416	156	Ψ 2.2 (1.8-2.7)
Progestin only	3,971	5	Ψ 1.7 (0.7-4.2)
Unknown	37,247	28	Ψ 0.9 (0.6-1.3)
Duration of estrogen only use (yrs)			
No use	288,904	222	1.0(reference)
<8	78,964	117	1.8 (1.4-2.3)
8-<16	11,591	59	6.4 (4.7-8.6)
≥16	2,937	33	15 (9.9-22)
Unknown	12,716	28	2.7 (1.8-4.1)
Hypertension			
Never	459,856	548	1.0 (reference)
Ever	47,732	77	1.0 (0.8-1.3)
Unsure	11,160	23	1.1 (0.7-1.7)
Diabetes			
Never	492,344	604	1.0 (reference)
Ever	11,695	19	0.9 (0.6-1.5)
Unknown	14,708	25	1.1 (0.7-1.6)
Smoking			
Never	321,55	394	1.0 (reference)
Current	60,175	43	0.7 (0.5-0.9)
Former	134,986	206	1.1 (0.9-1.3)
Unsure	2,024	5	1.5 (0.6-3.7)
Personal history of breast cancer			
Never	468,590	567	1.0 (reference)
Ever	50,157	81	1.3 (1.1-1.7)

Table 1. Rate ratios (RR) of endometrial cancer associated with selected factors in BCDDP endometrial cancer Follow-up Study, 1979-1998

Risk factor	No. of Person-Years	No. of Cases (n=648)	RR* (95% CI)
Age at menarche (yrs)			
<11	18,391	23	1.0 (reference)
11-12	193,246	267	1.1 (0.7-1.7)
13-14	239,642	291	1.0 (0.6-1.5)
>14	64,044	58	0.7 (0.5-1.2)
Unknown	3,424	9	2.8 (1.3-6.1)
Age at first live birth			
<25	252,127	288	1.0 (reference)
25-29	131,296	152	1.0 (0.8-1.2)
30-34	41,033	54	0.9 (0.7-1.3)
35-39	12,118	13	0.8 (0.4-1.4)
≥40	2,185	1	0.3 (0.0-2.2)
Age at last birth			
<30	136,404	165	1.0 (reference)
30-34	105,768	132	1.1 (0.9-1.4)
35-39	58,139	59	0.8 (0.6-1.1)
≥40	16,306	5	0.2 (0.1-0.6)
Unknown	195,004	272	1.1 (0.9-1.4)
Menopausal status			
Pre-menopause	65,740	24	1.0 (reference)
Menopause	437,138	608	1.4 (0.9-2.3)
Unknown	15,869	16	1.1 (0.6-2.6)
Age at natural Menopause			
<48	104,401	133	1.0 (reference)
48-49	81,253	94	1.0 (0.8-1.3)
50-51	99,727	138	1.2 (1.0-1.6)
52-54	106,507	140	1.2 (0.9-1.5)
>54	34,246	65	1.6 (1.1-2.1)

*All analyses are adjusted for attained age, menopausal status, BMI, duration of estrogen use, parity, and personal breast cancer diagnosis. If the risk factor included one of these factors, that variable was taken out of the model.

Ψ Relative risks were not adjusted for duration of estrogen use.

Table 2. Prevalence of first-degree family history of breast cancer according to selected factors in BCDDP endometrial cancer Follow-up Study, 1979-1998

Risk factor	Never 1st degree family history of breast cancer (%)	Ever 1st degree family history of breast cancer (%)	Unsure 1st degree family history of Breast cancer (%)	Total person-years
Attained age (yrs)				
<50	85.0	14.0	1.0	47,881
50-54	83.1	15.4	1.6	72,040
55-59	81.6	16.5	1.9	100,680
60-64	80.3	17.7	2.0	101,318
65-69	78.9	19.0	2.1	82,058
70-74	77.7	20.1	2.2	55,842
75+	75.7	21.8	2.5	58,927
Education				
<High school	81.6	16.3	2.1	61,610
High school	80.7	17.3	2.0	209,637
Some college	80.1	18.0	1.9	121,173
College graduate +	79.7	18.6	1.7	122,025
Unknown	72.7	25.2	2.0	4,302
Race				
White	79.7	18.3	1.9	451,128
Hispanic	85.2	12.5	2.3	11,692
Black	83.7	14.5	1.7	19,998
Other	84.6	13.8	1.6	35,930
Body mass index (kg/m^2)				
<22.05	81.1	17.3	1.6	185,058
22.06-25.07	80.3	17.6	2.1	154,982
25.08-27.85	79.8	18.2	2.0	80,203
27.86-32.06	79.6	18.1	2.3	53,369
32.07+	78.8	19.0	2.2	26,508
Unknown	79.6	18.6	1.8	18,625
Parity				
0	80.2	17.8	1.9	79,425
1	81.1	17.0	1.9	63,325
2	80.4	17.7	1.9	151,881
≥3	80.2	17.9	1.9	224,116
Oral contraceptive use				
Never	80.1	17.9	1.9	364,369
Ever	80.9	17.2	1.9	153,724
Unknown	70.2	17.3	12.5	654

Table 2. Prevalence of first-degree family history of breast cancer according to selected factors in BCDDP endometrial cancer Follow-up Study, 1979-1998

Risk factor	Never 1st degree family history of breast cancer (%)	Ever 1st degree family history of breast cancer (%)	Unsure 1st degree family history of Breast cancer (%)	Total person-years
Duration of oral contraceptive use				
No use	80.1	18.0	1.9	364,967
<3	80.6	17.6	1.8	73,976
3-<9	80.6	17.6	1.8	50,216
≥9	82.3	15.6	2.1	25,776
Unknown	82.3	14.7	3.0	3,182
Estrogen/estrogen-progestin (ERT-PRT) use				
No use	80.8	17.6	1.6	303,995
Estrogen only	80.7	17.4	1.9	91,118
Estrogen-progestin/ PRT (estrogen unknown)	79.8	17.7	2.5	82,416
Progestin only	79.7	17.8	2.5	3,971
Unknown	77.2	20.0	2.8	37,247
Duration of estrogen only use (yrs)				
No use	80.7	17.6	1.6	288,904
<8	81.8	16.4	1.8	78,964
8-<16	77.6	20.5	1.9	11,591
≥16	77.0	21.0	2.0	2,937
Unknown	79.0	18.7	2.3	12,716
Hypertension				
Never	80.6	17.5	1.8	459,856
Ever	79.0	18.5	2.5	47,732
Unsure	75.0	22.3	2.9	11,160
Diabetes				
Never	80.6	17.6	1.8	492,344
Ever	75.6	21.8	2.6	11,695
Unknown	77.4	19.3	3.3	14,708
Smoking				
Never	81.1	17.1	1.8	321,562
Current	81.5	16.8	1.7	60,175
Former	78.0	19.7	2.3	134,986
Unsure	75.6	20.0	4.4	2,024
Personal history of breast cancer				
Never	81.3	16.8	1.9	468,590
Ever	71.4	26.3	2.3	50,157

Table 2. Prevalence of first-degree family history of breast cancer according to selected factors in BCDDP endometrial cancer Follow-up Study, 1979-1998

Risk factor	Never 1st degree family history of breast cancer (%)	Ever 1st degree family history of breast cancer (%)	Unsure 1st degree family history of Breast cancer (%)	Total person-years
Age at menarche (yrs)				
<11	80.7	17.4	1.9	18,391
11-12	80.4	17.6	2.0	193,246
13-14	80.4	17.9	1.7	239,642
>14	80.0	17.9	2.1	64,044
Unknown	81.0	16.0	3.0	3,424
Age at first live birth				
<25	80.8	17.2	2.0	252,127
25-29	80.4	17.8	1.8	131,296
30-34	78.3	20.1	1.7	41,033
35-39	80.1	18.2	1.7	12,118
≥40	75.0	23.7	1.3	2,185
Age at last birth				
<30	80.7	17.3	2.0	136,404
30-34	79.0	19.0	2.0	105,768
35-39	70.5	18.6	1.9	58,139
≥40	79.0	19.4	1.6	16,306
Unknown	81.2	16.9	1.9	195,004
Menopausal status				
Pre-menopause	83.5	15.1	1.4	65,740
Menopause	79.9	18.1	2.0	437,138
Unknown	79.9	17.3	2.8	15,869
Age at natural Menopause				
<48	81.0	17.2	1.8	104,401
48-49	80.0	18.3	1.7	81,253
50-51	80.3	17.8	1.9	99,727
52-54	79.3	18.5	2.2	106,507
>54	77.0	20.6	2.5	34,246

Table 3. Rate ratios (RR) of endometrial cancer among women with a personal history of breast cancer associated with family history of breast cancer in BCDDP endometrial cancer Follow-up Study, 1979-1998

Relative	No. of Person-Years	No. of Cases	Adjusted* RR (95%CI)
Any family history			
No history	22,813	35	1.0 (reference)
1 affected	13,266	23	0.9 (0.5-1.6)
2 or more affected	6,781	9	0.8 (0.4-1.6)
Any affected	20,047	32	0.9 (0.5-1.4)
Unknown	7,298	14	0.8 (0.4-1.6)
Any 1st degree			
No history	35,823	60	1.0 (reference)
1 affected	10,651	18	0.9 (0.5-1.6)
2 or more affected	2,522	2	0.5 (0.1-2.1)
Any affected	13,173	20	0.9 (0.5-1.4)
Unknown	1,161	1	0.5 (0.0-3.8)
1st and 2nd degree			
No history	22,851	35	1.0 (reference)
Any affected	3,580	5	0.7 (0.3-1.8)
Unknown	10,203	20	0.9 (0.5-1.6)

* Adjusted for number of relatives, attained age, BMI, race, menopausal status.
Women who did not have relatives with breast cancer in that category formed the reference group for each row.

Table 4. Rate ratios (RR) of endometrial cancer associated with family history of breast cancer in BCDDP endometrial cancer Follow-up Study, 1979-1998 [case 1 definition]

Relative	No. of Person-Years	No. of Cases	Adjusted* RR (95%CI)
Any family history	140,762	173	0.9 (0.8-1.1)
1 affected	99,161	120	0.9 (0.7-1.1)
2 or more affected	41,601	53	0.9 (0.7-1.2)
Unknown	69,797	78	0.7 (0.6-0.9)
Any 1st degree	81,720	103	1.0 (0.8-1.2)
1 affected	69,799	89	1.0 (0.8-1.2)
2 or more affected	11,920	14	0.9 (0.5-1.5)
Unilateral	40,442	43	0.8 (0.6-1.1)
Bilateral	7,926	14	1.4 (0.8-2.4)
Unknown	34,087	46	1.1 (0.8-1.5)
Any 2nd degree	80,864	101	1.0 (0.8-1.2)
1 affected	62,150	72	0.9 (0.7-1.2)
2 or more affected	18,715	29	1.2 (0.8-1.8)
Unknown	85,970	104	0.9 (0.7-1.1)

* Adjusted for number of relatives, attained age, BMI, personal history of breast cancer, race, menopausal status.
Women who did not have relatives with breast cancer in that category formed the reference group for each row.

Table 5. Rate ratios (RR) of endometrial cancer associated with family history of breast cancer in BCDDP Endometrial Cancer Follow-up Study, 1979-1998 [case 3 definition]

Relative	No. of Person-Years	No. of Cases	Adjusted* RR (95%CI)
Any family history	140,766	155	0.9 (0.7-1.1)
1 affected	99,165	110	0.9 (0.7-1.1)
2 or more affected	41,601	45	0.8 (0.6-1.1)
Unknown	69,810	70	0.7 (0.5-0.9)
Any 1st degree	81,720	94	1.0 (0.8-1.2)
1 affected	69,800	83	1.0 (0.8-1.3)
2 or more affected	11,921	11	0.7 (0.4-1.4)
Unilateral	40,442	41	0.8 (0.6-1.2)
Bilateral	7,927	13	1.5 (0.9-2.6)
Unknown	34,088	40	1.0 (0.7-1.4)
Any 2nd degree	80,868	89	0.9 (0.7-1.2
1 affected	62,153	62	0.9 (0.6-1.1)
2 or more affected	18,715	27	1.2 (0.8-1.8)
Unknown	85,984	92	0.8 (0.7-1.1)

* Adjusted for number of relatives, attained age, BMI, personal history of breast cancer, race, menopausal status.
Women who did not have relatives with breast cancer in that category formed the reference group for each row.

Table 6. Rate ratios (RR) of endometrial cancer associated with family history of breast cancer in BCDDP endometrial cancer Follow-up Study, 1979-1998 [case 4 definition]

Relative	No. of Person-Years	No. of Cases	Adjusted* RR (95%CI)
Any family history	157,024	179	0.9 (0.7-1.1)
1 affected	111,372	128	0.9 (0.7-1.1)
2 or more affected	45,653	51	0.8 (0.6-1.1)
Unknown	78,363	91	0.8 (0.6-1.0)
Any 1st degree	91,982	110	1.0 (0.8-1.2)
1 affected	78,650	98	1.0 (0.8-1.3)
2 or more affected	13,331	12	0.7 (0.4-1.2)
Unilateral	40,442	43	0.8 (0.6-1.1)
Bilateral	7,926	14	1.4 (0.8-2.4)
Unknown	34,087	46	1.1 (0.8-1.5)
Any 2nd degree	88,770	102	1.0 (0.8-1.2)
1 affected	68,461	74	0.9 (0.7-1.2)
2 or more affected	20,309	28	1.1 (0.8-1.7)
Unknown	96,429	118	0.9 (0.7-1.1)

* Adjusted for number of relatives, attained age, BMI, personal history of breast cancer, race, menopausal status.
Women who did not have relatives with breast cancer in that category formed the reference group for each row.

Table 7. Rate ratios for endometrial cancer, 95% Confidence Intervals, number of cases and total person-years, according to history of breast cancer in mother and sister(s) by characteristics of the case

Mother with Breast Cancer	Sister(s) with Breast Cancer		Age at Diagnosis		Estrogen Use		BMI (kg/m^2)		Menopausal status	
		Overall	<60	≥60	Yes	No	>28	<28	Yes	No
No	No	1.0 524/ 419,600	1.0 88/ 70,362	1.0 436/ 349,238	1.0 163/ 74,132	1.0 207/ 247,100	1.0 385/ 340,820	1.0 121/ 63,829	1.0 488/ 351,629	1.0 23/ 55,226
Yes	No	1.0 (0.7-1.3) 56/ 44,184	0.7 (0.3-1.6) 7/ 7,423	1.0 (0.8-1.4) 49/ 36,761	1.3 (0.8-2.1) 19/ 6,556	0.9 (0.6-1.4) 20/ 26,189	0.9 (0.7-1.3) 38/ 35,424	1.0 (0.6-1.7) 15/ 7,171	1.0 (0.7-1.3) 50/ 35,333	1.0 (0.3-3.3) 3/ 7,172
No	Yes	1.0 (0.7-1.3) 52/ 38,233	0.6 (0.3-1.5) 7/ 6,357	1.0 (0.7-1.4) 45/ 31,876	0.9 (0.5-1.5) 16/ 7,368	1.0 (0.6-1.6) 21/ 21,843	1.2 (0.8-1.6) 43/ 30,689	0.4 (0.1-0.9) 5/ 6,044	1.0 (0.7-1.3) 52/ 35,174	--- 0/ 2,216
Yes	Yes	0.8 (0.4-1.6) 7/6,126	1.5 (0.4-4.9) 3/1,065	0.5 (0.2-1.4) 4/5,062	0.7 (0.2-2.5) 3/1,091	0.9 (0.3-2.8) 3/3,628	0.6 (0.2-1.7) 4/5,038	0.9 (0.2-3.6) 2/895	0.8 (0.4-1.6) 7/5,461	--- 0/518

All the analyses are adjusted for attained age, race, menopausal status, BMI, number of sisters, and personal history of breast cancer; when the analysis was stratified by one of these variables, that variable was taken out of the model.

Each reference group includes women with no history of breast cancer in either mother or sister(s).

Table 8. Rate ratios for endometrial cancer, 95% Confidence Intervals, number of cases and total person-years by family history and age at natural menopause

Age at Natural Menopause	1st degree Family History		Mother's History		Sister's History	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**
< 48	1.0	1.1 (0.7-1.7)	1.0	0.9 (0.5-1.7)	1.0	1.0 (0.6-1.6)
	104/85,998	26/18,142	119/95,111	11/9,178	115/95,097	22/16,360
48-49	1.0 (0.7-1.3)	0.8 (0.5-1.4)	0.9 (0.7-1.2)	1.0 (0.5-1.8)	0.9 (0.7-1.2)	1.0 (0.6-1.6)
	76/67,823	16/15,331	83/74,994	10/8,279	84/76,050	21/16,499
50-51	1.1 (0.9-1.5)	0.9 (0.6-1.4)	1.1 (0.9-1.4)	0.87 (0.5-1.6)	1.1 (0.8-1.4)	1.0 (0.7-1.6)
	116/85,733	22/18,581	127/94,435	11/9,898	125/95,650	25/18,971
52-54	0.9 (0.7-1.2)	1.1 (0.7-1.7)	1.0 (0.7-1.2)	0.9 (0.5-1.6)	0.9 (0.7-1.2)	1.0 (0.6-1.7)
	106/95,064	31/21,668	123/105,015	14/11,961	123/106,909	20/15,626
≥55	1.3 (1.0 – 1.9)	1.3 (0.7-2.4)	1.3 (0.9-1.7)	1.4 (0.7-3.1)	1.3 (1.0-1.8)	1.5 (0.7-3.2)
	53/32,501	13/8,477	59/36,478	7/4,531	59/37,177	7/5,622

All the analyses are adjusted for attained age, race, BMI, family size, and personal history of breast cancer.
Each reference group includes women who did not have relatives with breast cancer in that category and who had the lowest risk level of the other factor (age at natural menopause).

Table 9. Rate ratios for endometrial cancer, 95% Confidence Intervals, number of cases and total person-years by family history and parity

Parity	1st degree Family History		Mother's History		Sister's History	
	No	Yes	No	Yes	No	Yes
Nulliparous	1.0	0.7 (0.4-1.1)	1.0	0.6 (0.3-1.1)	1.0	0.8 (0.4-1.4)
	118/63,731	18/14,157	129/70,407	8/7,620	124/70,736	12/76,13
1	0.7 (0.5-1.0)	0.6 (0.4-1.1)	0.7 (0.6-1.0)	0.6 (0.3-1.3)	0.7 (0.6-1.0)	0.6 (0.3-1.4)
	68/51,348	13/10,754	75/56,759	6/5,430	74/56,794	7/5,820
2	0.7 (0.6-0.9)	0.9 (0.6-1.2)	0.8 (0.6-1.0)	0.9 (0.5-1.4)	0.8 (0.6-1.0)	0.8 (0.5-1.3)
	159/122,061	42/26,942	178/134,151	23/15,039	183/137,045	19/12,996
3	0.6 (0.5-0.8)	0.6 (0.4-0.9)	0.6 (0.5-0.7)	0.6 (0.4-0.9)	0.6 (0.5-0.7)	0.6 (0.4-1.0)
	176/179,699	46/40,128	195/197,650	27/22,490	202/202,778	21/18,583

All the analyses are adjusted for attained age, race, BMI, menopausal status, family size, and personal history of breast cancer.

Each reference group includes women who did not have relatives with breast cancer in that category and who had the lowest risk level of the other factor (nulliparous).

Table 10. Prevalence of first-degree family history of breast cancer according to selected factors in BCDDP ovarian cancer Follow-up Study, 1979-1998

Risk factor	Never 1st degree family history of breast cancer (%)	Ever 1st degree family history of breast cancer (%)	Unsure 1st degree family history of Breast cancer (%)	Total person-years
Attained age (yrs)				
<50	85.3	13.7	1.0	63,176
50-54	83.1	15.3	1.6	98,312
55-59	81.5	16.6	1.9	138,368
60-64	80.1	17.9	2.1	140,050
65-69	78.6	19.2	2.2	114,298
70-74	77.1	20.6	2.3	78,548
75+	75.1	22.4	2.5	83,161
Education				
<High school	81.0	16.9	2.1	91,910
High school	80.3	17.7	2.0	293,490
Some college	79.9	18.1	2.0	168,207
College graduate +	79.5	18.7	1.8	156,047
Unknown	74.8	23.2	2.0	6,259
Race				
White	79.5	18.6	2.0	620,635
Hispanic	84.6	13.4	2.1	16,852
Black	84.1	13.8	2.1	32,873
Other	84.1	14.2	1.8	45,553
Body mass index (kg/m^2)				
<22.05	80.8	17.6	1.7	247,203
22.06-25.07	80.0	18.0	2.0	213,613
25.08-27.85	79.7	18.2	2.1	113,661
27.86-32.06	79.4	18.1	2.4	77,402
32.07+	78.8	18.7	2.5	38,653
Unknown	79.4	18.6	2.0	25,382
Parity				
0	80.0	18.0	2.0	98,392
1	80.1	17.8	2.1	85,240
2	80.2	17.9	1.9	208,699
≥3	80.1	18.0	1.9	323,582
Oral contraceptive use				
Never	79.8	18.2	2.0	502,233
Ever	80.8	17.2	1.9	212,658
Unknown	75.7	15.3	9.0	1,022

Table 10. Prevalence of first-degree family history of breast cancer according to selected factors in BCDDP ovarian cancer Follow-up Study, 1979-1998

Risk factor	Never 1st degree family history of breast cancer (%)	Ever 1st degree family history of breast cancer (%)	Unsure 1st degree family history of Breast cancer (%)	Total person-years
Duration of oral contraceptive use				
No use	79.8	18.2	2.0	503,132
<3	80.7	17.5	1.8	105,796
3-<9	80.6	17.6	1.8	69,198
≥9	81.8	16.2	2.0	32,203
Unknown	81.9	14.5	3.6	5,585
Estrogen/estrogen-progestin (ERT-PRT) use				
No use	80.5	17.8	1.7	357,789
Estrogen only	80.0	18.0	2.0	206,671
Estrogen-progestin/ PRT (estrogen unknown)	79.9	17.6	2.5	100,095
Progestin only	79.2	17.6	3.2	4,688
Unknown	77.4	19.7	2.9	46,671
Duration of estrogen only use (yrs)				
No use	80.5	17.8	1.7	344,158
<8	80.9	17.3	1.8	136,839
8-<16	78.7	19.1	2.2	33,475
≥16	78.8	19.2	2.0	19,087
Unknown	78.9	18.9	2.2	30,901
Smoking				
Never	80.7	17.4	1.9	448,308
Current	81.0	17.3	1.7	80,821
Former	78.1	19.6	2.3	183,955
Unsure	78.1	18.6	3.3	2,830
Personal history of breast cancer				
Never	81.1	17.0	1.9	647,592
Ever	70.9	26.7	2.4	68,321
Age at menarche (yrs)				
<11	80.1	17.6	2.3	27,274
11-12	80.3	17.6	2.0	271,845
13-14	80.0	18.2	1.8	325,257
>14	79.8	18.0	2.1	87,053
Unknown	79.0	18.0	3.0	4,485

Table 10. Prevalence of first-degree family history of breast cancer according to selected factors in BCDDP ovarian cancer Follow-up Study, 1979-1998

Risk factor	Never 1st degree family history of breast cancer (%)	Ever 1st degree family history of breast cancer (%)	Unsure 1st degree family history of Breast cancer (%)	Total person-years
Age at first live birth				
<25	80.5	17.4	2.1	374,653
25-29	79.9	18.2	1.8	173,194
30-34	78.2	20.2	1.6	51,872
35-39	78.8	19.2	2.0	14,491
≥40	77.7	21.1	1.2	2,523
Age at last birth				
<30	80.3	17.6	2.1	201,342
30-34	78.6	19.5	1.9	145,058
35-39	79.2	19.0	1.8	77,411
≥40	78.8	19.5	1.7	21,268
Unknown	81.1	16.9	1.9	260,944
Menopausal status				
Pre-menopause	80.6	17.5	1.9	249,232
Menopause	79.8	18.2	2.0	450,580
Unknown	80.0	17.2	2.8	16,102
Age at natural menopause				
<48	81.0	17.2	1.8	109,006
48-49	79.8	18.5	1.7	83,605
50-51	80.3	17.8	1.9	102,791
52-54	79.4	18.5	2.1	109,132
>54	77.0	21.0	2.0	35,547
Hysterectomy				
No	80.3	17.8	1.9	501,640
Yes	79.6	18.4	2.0	211,973
Unknown	80.0	14.0	6.0	2,300
Religion				
Catholic	80.0	17.9	2.0	161,090
Jewish	80.9	17.5	1.6	71,317
Mormon	78.7	19.1	2.2	9,162
7th day Adventist	79.6	18.0	2.4	2,353
Protestant	79.7	18.3	2.0	429,789
Other	83.3	15.0	1.7	36,327
Unknown	82.8	16.6	0.7	5,875

Table 11. Age adjusted relative risks (RR) of ovarian cancer associated with selected factors in BCDDP ovarian cancer Follow-up Study, 1979-1998

Risk factor	No. of Person-Years	No. of Cases (n=648)	RR (95% CI)
Attained age (yrs)			
<50	63,176	8	1.0 (reference)
50-54	98,312	30	0.9 (0.4-1.9)
55-59	138,368	67	1.0 (0.5-2.1)
60-64	140,050	63	0.7 (0.4-1.5)
65-69	114,298	58	0.8 (0.4-1.6)
70-74	78,548	64	0.7 (0.3-1.4)
75+	83,161	72	0.4 (0.2-0.9)
Education			
<High school	91,910	56	1.0 (reference)
High school	293,490	137	0.9 (0.7-1.2)
Some college	168,207	88	1.0 (0.7-1.4)
College graduate +	156,047	76	1.0 (0.7-1.4)
Unknown	6,259	5	1.6 (0.6-3.9)
Race			
White	620,635	330	1.0 (reference)
Hispanic	16,852	2	0.2 (0.0-0.9)
Black	32,873	14	0.8 (0.5-1.4)
Other	45,553	16	0.7 (0.4-1.1)
Body mass index (kg/m^2)			
<22.05	247,203	124	1.0 (reference)
22.06-25.07	213,613	121	1.0 (0.8-1.3)
25.08-27.85	113,661	50	0.8 (0.6-1.1)
27.86-32.06	77,402	37	0.9 (0.6-1.2)
32.07+	38,653	19	0.9 (0.6-1.5)
Unknown	25,382	11	0.8 (0.4-1.4)
Parity			
0	98,392	61	1.0 (reference)
1	85,240	61	1.2 (0.8-1.7)
2	208,699	102	0.9 (0.6-1.2)
≥3	323,582	138	0.8 (0.6-1.0)
Oral contraceptive use			
Never	502,233	293	1.0 (reference)
Ever	212,658	66	0.72 (0.54-0.95)
Unknown	1,022	3	5.5 (1.80-17.0)

Table 11. Age adjusted relative risks (RR) of ovarian cancer associated with selected factors in BCDDP ovarian cancer Follow-up Study, 1979-1998

Risk factor	No. of Person-Years	No. of Cases (n=648)	RR (95% CI)
Duration of oral contraceptive use			
No use	503,132	295	1.0 (reference)
<3	105,796	37	0.8 (0.6-1.1)
3-<9	69,198	19	0.6 (0.4-1.0)
≥9	32,203	8	0.6 (0.3-1.2)
Unknown	5,585	3	1.1 (0.4-3.5)
Estrogen/estrogen-progestin (ERT-PRT) use			
No use	357,789	152	1.0 (reference)
Estrogen only	206,671	136	1.4 (1.1-1.7)
Estrogen-progestin/ PRT (estrogen unknown)	100,095	47	1.0 (0.7-1.4)
Progestin only	4,688	1	0.5 (0.0-3.9)
Unknown	46,671	26	1.3 (0.9-1.9)
Duration of estrogen only use (yrs)			
No use	344,158	138	1.0 (reference)
<8	136,839	85	1.4 (1.0-1.8)
8-<16	33,475	20	1.3 (0.8-2.0)
≥16	19,087	20	2.0 (1.2-3.2)
Unknown	30,901	25	1.6 (1.1-2.5)
Smoking			
Never	448,308	237	1.0 (reference)
Current	80,821	26	0.8 (0.5-1.2)
Former	183,955	97	1.0 (0.8-1.3)
Unsure	2,830	2	1.1 (0.3-4.6)
Personal history of breast cancer			
Never	647,592	307	1.0 (reference)
Ever	68,321	55	1.5 (1.1-2.0)
Age at menarche (yrs)			
<11	27,274	12	1.0 (reference)
11-12	271,845	119	0.9 (0.5-1.7)
13-14	325,257	183	1.1 (0.6-2.0)
>14	87,053	45	1.0 (0.5-1.9)
Unknown	4,485	3	1.2 (0.3-4.2)

Table 11. Age adjusted relative risks (RR) of ovarian cancer associated with selected factors in BCDDP ovarian cancer Follow-up Study, 1979-1998

Risk factor	No. of Person-Years	No. of Cases (n=362)	RR (95% CI)
Age at first live birth			
<25	374,653	169	1.0 (reference)
25-29	173,194	96	1.1 (0.8-1.4)
30-34	51,872	29	1.0 (0.7-1.5)
35-39	14,491	6	0.7 (0.3-1.6)
≥40	2,523	1	0.6 (0.1-4.5)
Age at last birth			
<30	201,342	67	1.0 (reference)
30-34	145,058	47	0.7 (0.5-1.1)
35-39	77,411	17	0.5 (0.3-0.8)
≥40	21,268	4	0.4 (0.1-1.0)
Unknown	260,944	223	1.8 (1.3-2.4)
Menopausal status			
Pre-menopause	249,232	88	1.0 (reference)
Menopause	450,580	267	1.3 (1.0-1.7)
Unknown	16,102	7	1.1 (0.5-2.5)
Age at natural menopause			
<48	110,646	60	1.0 (reference)
48-49	86,925	46	1.0 (0.7-1.5)
50-51	109,321	52	0.9 (0.6-1.4)
52-54	121,778	70	1.2 (0.8-1.6)
>54	43,243	17	0.8 (0.5-1.3)
Hysterectomy			
No	501,640	273	1.0 (reference)
Yes	211,973	89	0.8 (0.6-1.0)
Unknown	2,300	0	---
Religion			
Catholic	161,090	82	1.0 (reference)
Jewish	71,317	44	1.1 (0.8-1.6)
Mormon	9,162	2	0.4 (0.1-1.7)
7th day Adventist	2,353	1	0.8 (0.1-5.7)
Protestant	429,789	213	0.9 (0.7-1.2)
Other	36,327	17	0.9 (0.5-1.5)
Unknown	5,875	3	1.0 (0.3-3.1)

Table 12. Rate ratios for ovarian cancer, 95% Confidence Intervals, number of cases and total person-years by age of diagnosis and disease laterality of relative with breast cancer

	Mother with Breast Cancer					
	Mother's Age at Diagnosis*			Mother's Laterality Status		
Reference Group	<50	≥50	Unknown	Unilateral	Bilateral	Unknown
1.0	1.1	0.9	1.6	1.1	1.1	1.2
	(0.5-2.7)	(0.6-1.5)	(1.0-2.7)	(0.7-1.8)	(0.3-3.3)	(0.8-1.9)
CA/PY	5/10,040	18/40,418	16/19,228	18/33,537	3/6,234	19/30,441
	Sister with Breast Cancer					
	Sister's Age at Diagnosis*			Sister's Laterality Status		
Reference Group	<50	≥50	Unknown	Unilateral	Bilateral	Unknown
1.0	1.5	0.8	1.4	0.5	1.5	1.7
	(0.8-2.6)	(0.5-1.5)	(0.9-2.4)	(0.2-1.0)	(0.6-3.6)	(1.2-2.5)
CA/PY	13/19,706	13/28,693	16/15,652	7/29,365	5/6,654	30/28,477
	Daughter with Breast Cancer					
	Daughter's Age at Diagnosis*			Daughter's Laterality Status		
Reference Group	<50	≥50	Unknown	Unilateral	Bilateral	Unknown
1.0	2.3	--	1.0	2.0	3.2	0.8
	(0.9-5.6)		(0.2-7.5)	(0.7-5.3)	(0.4-23)	(0.1-5.8)
CA/PY	5/3,787	0/627	11,349	4/3,506	1/476	1/1,746

* Age at diagnosis is the age of youngest relative in that category with breast cancer.
All analyses are adjusted for attained age, number of relatives in each category (except mother's category), and personal breast cancer diagnosis.
Women who did not have relatives with breast cancer in that category formed the reference group for each group.
CA= Number of cases; PY= Total person-years.

Table 13. Rate ratios of ovarian cancer associated with first-degree family history of breast, ovarian, and colorectal cancers among the sub-cohort (527,252 person-years) who completed the phase IV interview

Relative	No. of Person-Years	No. of cases	Adjusted * RR (95% CI)	
Family history of breast cancer				Adjusted for family history of ovarian cancer
No history	419,760	101	1.0 (reference)	1.0 (reference)
1 affected	82,493	15	0.7 (0.4-1.2)	0.7 (0.4-1.2)
2 or more affected	14,727	10	2.4 (1.2-4.6)	2.3 (1.1-4.4)
Any affected	97,221	25	1.0 (0.6-1.5)	0.9 (0.6-1.5)
Unknown	10,271	4	1.5 (0.5-4.0)	1.4 (0.5-3.9)
Family history of ovarian cancer				Adjusted for family history of breast cancer
No history	470,151	103	1.0 (reference)	1.0 (reference)
Any affected	27,086	16	2.8 (1.6-4.7)	2.9 (1.7-4.9)
Unknown	30,015	11	1.5 (0.8-2.8)	1.5 (0.8-2.8)
Family history of colorectal cancer				Adjusted for family history of breast cancer
No history	426,154	103	1.0 (reference)	1.0 (reference)
Any affected	69,030	17	1.0 (0.6-1.7)	1.0 (0.6-1.7)
Unknown	32,068	10	1.1 (0.6-2.2)	1.1 (0.6-2.2)

*All analyses are adjusted for attained age, personal breast cancer diagnosis, and number of first-degree relatives.

APPENDIX C

List of the state cancer registries used in the BCDDP endometrial and ovarian cancer Follow-up Studies, including their year restrictions

Arizona: none stated
California: 1988-1998
Florida: 1987-1999
Georgia: 1987-1997
Hawaii: none stated
Idaho: 1987-1998
Iowa: 1987-1997
Maryland: 1992-1995
Michigan: 1987-1997
New Jersey: none stated
New York: none stated
North Carolina: none stated
Ohio: 1991+
Oregon: none stated
Pennsylvania: 1987-1995
Rhode Island: none stated
Tennessee: none stated
Texas: none stated
Virginia: none stated